THE

MEDICAL CLINICS

OF

NORTH AMERICA

MAY, 1940

CONTRIBUTORS TO THIS NUMBER

VIRGINIA APGAR, M. D., Assistant Professor of Anesthesia, College of Physicians and Surgeons, Columbia University; Attending Anesthetist, Presbyterian and Babies Hospitals and Vanderbilt Clinic; Associate Attending Anesthetist, Welfare Hospital.

ALVAN L. BARACH, M. D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Assistant Attending Physician, Presbyterian Hospital.

HENRY ALFRED BARRETT, M. D., Chief, Department of Physical Therapy, Roosevelt Hospital; Assistant Roentgenologist, Manhattan Eye, Ear and Throat Hospital; Associate Visiting Roentgenologist, Willard Parker Hospital.

Z. BERCOVITZ, M. D., Assistant Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University; Instructor in Medicine, Cornell University Medical School; Assistant Attending Physician, New York Post-Graduate Hospital; Assistant Visiting Physician, Second Medical (Cornell) Division, Bellevue Hospital; Associate Visiting Physician, Welfare Island Hospital.

KARL M. BOWMAN, M. D., Professor of Psychiatry, New York University Medical College; Director of Psychiatric Division, Bellevue Hospital.

LINN J. BOYD, M. D., Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Director of Medicine, Metropolitan Hospital.

ALVIN F. COBURN, M. D., Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University; Assistant Attending Physician in Medicine, Presbyterian Hospital and Vanderbilt Clinic.

HENRY A. CROMWELL, M. D., Assistant in Medicine, Assistant Physician, Presbyterian Hospital and Vanderbilt Clinic.

JOHN KIMBERLY CURTIS, M. D., Assistant in Medicine, College of Physicians and Surgeons, Columbia University; Assistant Physician, Presbyterian Hospital and Neurological Institute.

ELVIRA GOETTSCH, M. D., Associate in Pediatrics, College of Physicians and Surgeons, Columbia University; Assistant Pediatrician, Babies Hospital.

HARRY GOLD, M. D., Assistant Professor of Pharmacology, Cornell University Medical College; Associate Physician and Chief of Cardiac Clinics, Beth Israel Hospital; Associate Physician and Chief of Cardiac Clinics, Hospital for Joint Diseases; Cardiologist, Sea View Hospital.

A. ALLEN GOLDBLOOM, M. D., Instructor in Medicine, New York Medical College, Hospital and Associate Physician, Metropolitan Hospital; Associate Physician and Associate Cardiologist, Beth Israel Hospital.

WALTER GOLDFARB, M. D., Assistant, Department of Psychiatry, New York University Medical College; Assistant Alienist, Bellevue Hospital, Psychiatric Division.

FRANZ M. GROEDEL, M. D., Consultant Cardiologist, Einhorn Department, Lenox Hill Hospital; Attending Cardiologist, Beth David Hospital.

I. W. HELD, M. D., Clinical Professor of Medicine, New York University College of Medicine; Attending Physician, Beth Israel Hospital.

CATHERINE A. ILLYNE, B. A., Research Department of Hematology, College of Physicians and Surgeons, Columbia University.

NORMAN JOLLIFFE, M. D., Associate Professor of Medicine, New York University College of Medicine; Chief of Medical Service, Psychiatric Division, Bellevue Hospital

BRUNO KISCH, M. D., Chief of Department of Experimental Medicine, Beth Israel Hospital, Attending Physiologist, Beth David Hospital.

YALE KNEELAND, Jr., M. D., Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University.

ABRAHAM LIEBERSON, M. D., Adjunct Physician and Assistant Cardiologist, Beth Israel Hospital; Clinical Assistant Visiting Physician, Second (Cornell) Division, Bellevue Hospital.

CONTRIBUTORS TO THIS NUMBER

JOHN B. LUDDEN, M. D., New York City.

JOHN DOOLEY LYTTLE, M. D., Assistant Clinical Professor of Pediatrics, College of Physicians and Surgeons, Columbia University; Assistant Attending Pediatrician, Babies Hospital.

HENRY ELSNER MARKS, M. D., Instructor in Medicine, College of Physicians and Surgeons, Columbia University; Associate Attending Physician, New York City Hospital; Assistant Physician, Vanderbilt Clinic.

DONOVAN JAMES McCUNE, M. D., Assistant Professor of Pediatrics, College of Physicians and Surgeons, Columbia University; Assistant Attending Pediatrician, Babies Hospital.

THOMAS HODGE McGAVACK, M. D., Associate Professor of Medicine, New York Medical College; Visiting Physician, Flower and Fifth Avenue Hospitals and Metropolitan Hospital.

ADE T. MILHORAT, M. D., Assistant Professor of Medicine, Cornell University Medical College; Research Fellow, Russell Sage Institute of Pathology; Assistant Attending Physician, New York Hospital.

LUCILLE V. MOORE, M. D., Instructor in Medicine, College of Physicians and Surgeons, Columbia University; Assistant Physician in Medicine, Presbyterian Hospital and Vanderbilt Clinic.

ROBERT CLINTON PAGE, M. D., Junior Assistant Physician, New York Post-Graduate Hospital; Clinical Assistant, Division of Internal Medicine, Grasslands Hospital, Valhalla, N. Y.

GEORGE SCHAEFER, M. D., Resident in Surgery, Gynecology and Obstetrics, Sea View Hospital, Staten Island, N. Y.

DAVID SCHERF, M. D., Associate Clinical Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Associate Visiting Physician and Cardiologist, Metropolitan Hospital.

MAX SCHNEIDER, M. D., Associate Gynecologist and Obstetrician, Sydenham Hospital; Adjunct Gynecologist, Beth Israel Hospital.

SAMUEL SILBERT, M. D., Adjunct Surgeon, Mount Sinai Hospital, Associate Surgeon, Montefiore Hospital.

EDMOND GEORGE THOMAS, B. A., New York City.

WILLIAM PAYNE THOMPSON, M. D., Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University.

JANET TRAVELL, M. D., Instructor in Pharmacology, Cornell University Medical College; Assistant Visiting Physician (Cardiology), Sea View Hospital.

NORMAN TREVES, M. D., Associate Attending Surgeon, Memorial Hospital; Consulting Surgeon and Radiologist, Tumor Clinic, Meadowbrook Hospital, Hempstead, N. Y.; Consulting . , eases) Nassau Hospital, Mineola, N. Y.; Consultant ', . ', ' ry Community Hospital, Glen Cove, N. Y.; Director, Huntington, N. Y.

ALEXANDER ASHLEY WEECH, M. D., Associate Professor of Pediatrics, College of Physicians and Surgeons, Columbia University; Attending Pediatrician, Babies Hospital.

ALEXANDER S. WIENER, M. D., Serologist and Bacteriologist to the Office of the Chief Medical Examiner of New York City; Head of the Division of Blood Transfusion, Jewish Hospital, Brooklyn, N. Y.; Lecturer in Forensic Medicine, New York University College of Medicine.

JOSEPH WORTIS, M. D., Research Fellow, Department of Psychiatry, New York University Medical College; Research Fellow, Bellevue Hospital, Psychiatric Division.

IRVING S. WRIGHT, M. D., Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University.

CONTENTS

SYMPOSIUM ON RECENT ADVANCES IN THERAPY

CLINICS ON OTHER SUBJECTS

CLINIC OF DR. HARRY GOLD

DEPARTMENT OF PHARMACOLOGY, CORNELL UNIVERSITY
MEDICAL COLLEGE

TREATMENT OF CARDIAC ARRHYTHMIAS

General Remarks Concerning Rational Therapeutics.
—In a volume such as this, dealing largely with progress in therapeutics, it is appropriate to consider briefly the method by which the efficacy of therapeutic agents in the treatment of disease is established. How can one ascertain when the changes which follow the use of a drug are due to the specific action of the drug? This question arises because of the well known fact that symptoms tend to subside and diseases tend to resolve as the result of innumerable factors so complex as to defy solution, which in the depth of our ignorance we refer to as "spontaneous" cures.

There are in essence two methods for dealing with this problem: In one of these the link between causes and effects is forged by the instinctive judgment of the medical practitioner. The physician follows his natural bent for adventure in therapeutics. He seizes upon suggestions, he gives them a clinical trial, he gains impressions and elaborates them into convictions. This method of determining the usefulness of an agent is ancient and very widely pursued. It is all we had until recent years. Much valuable knowledge has been acquired in this way. On the other hand, it has been instrumental if not chiefly responsible for the development also of large dispensatories describing thousands of therapeutic items

and massive formularies in which these are juggled together into mixtures mostly without semblance of reason. These issues are not good, at least not good enough, for the serious student of rational therapeutics.

The second method by which therapeutic knowledge develops involves the scientifically controlled clinical investigation. It is the method of the laboratory, but is no longer confined to the laboratory. The high standards of organization in specialized hospital services, and certain types of outpatient clinics, have placed at the disposal of the student of therapeutics facilities and clinical material suitable for investigation by technics as accurate and faultless in their control as the technics of the laboratory. This method is applicable to the study of all kinds of therapeutic agents: Comparison of the barbituric acid compounds, the newer volatile anesthetics, the various agents recently developed for the treatment of peptic ulcer, the vitamins, the endocrine materials, new metal preparations in the treatment of syphilis, chemotherapeutic agents such as sulfanilamide and related compounds in various types of infections—to mention but a few of the important fields in which great discoveries of scientific interest and practical importance have been made during recent years.

A point which requires emphasis, particularly in a period of great achievement by chemists in the field of therapeutics, is the fact that a wide gap exists between the *development* of a potent chemical product and the discovery of the *uses* to which it can be put in clinical therapeutics. If one takes an historical view of the matter, one finds that this gap is often filled by vague and inconclusive clinical impressions. A few seemingly satisfactory results in a few badly controlled cases with a new preparation produces in the mind of the physician a conviction of merits that do not exist. A striking example is the optimistic clinical literature on the superiority of ergotamine over the crude fluidextract or infusion of ergot for the prevention of postpartum hemorrhage. These clinical impressions accumulated during a period of about fifteen years, received a rude jolt when it was discovered by a sound clinical experiment that ergotamine exerts but a negligible action on the postpartum uterus and that a different alkaloid present in ergot is responsible for the uterine action. The favorable

"clinical experiences" with glandular preparations in disorders of the sex sphere received a serious setback in the early twenties when it was shown that the materials with which such supposedly striking therapeutic effects were obtained were, for the most part, inert. At present a somewhat different situation prevails in the therapy of sex disorders. Chemists have succeeded in making many potent materials available. This has by no means solved the problems. Now that we have these potent materials, there is little precise knowledge as to what to do with them, a state of uncertainty that is not, however, reflected in the abundant literature of commerce which in these days plays an influential rôle in directing therapeutic practices. The time has come when the uncompromising demands of a scientific clinical experiment may be made in the case of most therapeutic agents before one puts them to use in practice. The power of this method of evaluating a therapeutic agent is demonstrated by the numerous examples which might be cited in which one controlled clinical investigation has sufficed to blast a therapeutic practice based upon cherished clinical belief of a half century or more. The practitioner is unable to make these systematic studies in the course of his daily practice, but he can make a very considerable contribution to this problem by raising the standards of his demands of a preparation before he employs it. Practice with a limited number of potent agents, the value of which does not depend upon a large mass of clinical impressions but rests securely on the unequivocal results of a few thoroughly controlled clinical investigations, seems to be the direction in which enlightened therapeutics is moving. In this direction there lies the highest welfare of the patient. It also affords a basis for the highest professional and cultural development of the physician.

The discovery of new compounds presents the most dramatic and most intriguing aspect of therapeutic progress. However, it is not the sole index of progress. A very considerable part of genuine advance lies in the development of technics by which older drugs of established value may be best put to use. This aspect of therapeutic advance was uppermost in the mind of the writer in presenting the account which follows of the treatment of five of the more important types of abnormal rhythm of the heart:

Important Types of Abnormal Cardiac Rhythm.—

1. Paroxysmal auricular tachycardia.
2. Auricular flutter.
3. Auricular fibrillation.
4. Ventricular tachycardia.
5. Heart block, with Adam-Stokes attacks.

Although the title of this paper is often applied to the subject matter I propose to present, it is perhaps not strictly accurate, since most of the disorders of rhythm are not arrhythmic at all. The only one of the five which is practically always arrhythmic is auricular fibrillation.

Therapy in these rhythms is on a fairly high scientific plane. It represents one of the most highly developed phases of cardiac practice. Effective treatment depends directly upon important developments in physiology and pharmacology relating to the mechanism of the heart beat, and to perversions of the normal mechanism.

Differential Diagnosis.—An accurate differential diagnosis is extremely important in these cases, particularly a diagnosis which discloses the abnormal physiologic mechanism which drives the heart in the particular case. A treatment which is very effective in one form of disturbed rhythm may be either entirely ineffective in another or may even be dangerous. A good example is auricular and ventricular tachycardia. Both have rapid pulse rate, and they are clinically sometimes quite indistinguishable. What is effective against paroxysmal auricular tachycardia may even prove disastrous in the ventricular type. I shall refer to this again.

Mention should be made of the way in which physicians often *describe* disturbances of rhythm. To describe a disorder of heart action as "slow," "rapid," "regular," or "irregular," tells us virtually nothing about the nature of the mechanisms which drive the heart. Several of the fundamental disorders of rhythm, varying significantly in their mechanisms and in their response to drugs, may be rapid, or regular, or irregular. Auricular fibrillation, which is the most irregular of all rhythms, is sometimes clinically indistinguishable from the irregular rhythm of auricular flutter with varying block. They also respond differently to drugs. An extreme grade of sinus irregularity, a condition which requires no treatment at all,

is occasionally difficult to distinguish clinically from cases of auricular fibrillation. Many other examples could be cited of the utter inadequacy, as a basis for treatment, of the description of disturbed rhythms as "regular," "irregular," or "rapid." I emphasize this point because we encounter experiences rather frequently of patients who have been treated for an irregular heart or a rapid heart action, without the establishment of the *precise mechanism* which has rendered the heart irregular or rapid.

The differential diagnosis should be made on a *physiologic* basis: Where is the focus which drives the heart? Is it an interrupted discharge or a circus movement? These are not academic questions, but are directly related, as we shall see, to the matter of treatment.

The Electrocardiogram.—Not infrequently a differential diagnosis can be made solely by clinical means. In paroxysmal auricular tachycardia, the response to carotid sinus pressure, when it is typical, is characteristic of this condition alone, and if the classical response is obtained, we can rest assured that we have been dealing with paroxysmal auricular tachycardia, for no other condition gives this response.

In most instances, however, an electrocardiogram is necessary to establish the diagnosis and to insure effective as well as safe treatment. If we try to proceed to treat without an electrocardiographic diagnosis, we may be fortunate enough to abolish the abnormal rhythm, but it will be merely a matter of good luck, and we also stand a good chance of using the wrong treatment; of giving, for example, large doses of digitalis to a patient with ventricular tachycardia under the mistaken idea that it is an auricular flutter or a paroxysmal tachycardia. The result may be disastrous, since ventricular tachycardia may be made worse by digitalis, certainly not better.

When one refers to the "electrocardiographic diagnosis" in the differentiation of various disorders of rhythm, one should make it clear that the electrocardiogram alone is not enough. It alone more often fails to differentiate them in a significant manner than it succeeds. A tracing should be made *before* and *during carotid sinus pressure*. A patient presenting a rapid regular tachycardia of, let us say, 150 to 175 a minute,

may have either sinus tachycardia, paroxysmal auricular tachycardia, auricular flutter, or ventricular tachycardia. The tracing alone often leaves us in great doubt as to which of these it is, because the rhythm is so rapid that in the standard tracing we cannot discover what the auricle is doing. Its deflection is buried somewhere in the ventricular deflection. By the application of carotid sinus pressure, we may slow matters up, making it easier to analyze the events. In one case we may slow both the auricle and ventricle moderately. This clinches the diagnosis of sinus tachycardia. Or we may bring both the auricle and ventricle to a complete fleeting standstill. That confirms the diagnosis of paroxysmal auricular tachycardia. By the same procedure, only the ventricle may be brought to a standstill, and the tracing will show the auricle beating at 350 or so a minute. That helps to establish the diagnosis of auricular flutter. Or the carotid test may produce no effect upon either the auricle or the ventricle, in which case, depending upon the nature of the ventricular groups in the electrocardiogram, the rhythm turns out to be one of ventricular tachycardia.

There are several situations that are somewhat more complex than the ones I have just cited, but we may at present only emphasize the fact that when one has an electrocardiogram taken for a differential diagnosis of a disturbance of rhythm, one should in most instances have part of the tracing taken during the application of carotid sinus pressure. The results of the tracing will prove infinitely more instructive from the standpoint of differential diagnosis. So often, as I have indicated, the simple tracing alone leaves one no better equipped for the treatment of a case of tachycardia than the clinical examination without the tracing. And that leaves one almost completely in the dark.

At this point we may state that none of these disturbances of rhythm is confined to any special type of heart. All of them may be seen in hearts that are otherwise normal, in patients who are in all respects, so far as we can tell, normal, and all of them may also be seen arising in the course of the various types of heart disease, without exception.

Mechanisms for Sending Motor Vagal Impulses to the Heart.—I have already indicated that we can utilize a

vagal stimulus to the heart in the differential diagnosis of disorders of rhythm, because vagal stimulation does not have the same effect in the different disorders of rhythm. It has no influence in ventricular tachycardia. It stops the whole heart in paroxysmal auricular tachycardia. It stops only the ventricle in auricular flutter.

How can we make impulses pass down the motor fibers of the vagus to the heart? There are various methods, one of which I have already referred to:

1. Carotid sinus pressure.
2. Ocular pressure: Deep pressure over the eyeballs.
3. Deep inspiration: Holding the breath as long as possible.
4. Straining: Deep expiration with glottis closed as long as possible.
5. Increase the venous pressure in the head by lying across the bed with the head hanging over the side of the bed, or a table.

I have referred to the use of the carotid sinus test during the taking of the electrocardiogram. There are times when it will fail and one of the other methods for increasing vagal impulses going to the heart should be tried during the taking of the electrocardiogram, in order to secure a record of the events in the heart during high vagal activity.

Drugs.—The specific drugs that are useful in the treatment of disorders of cardiac rhythm are very few in number. The more important ones are:

1. Quinidine.
2. Digitalis.
3. Mecholyl.
4. Emetics (syrup of ipecac, apomorphine).

Agents that are less important, but of some value in certain individuals, are the *sedatives* such as the barbituric acid compounds or the bromides. There are also certain agents that are applicable to a few special cases: *ephedrine, barium chloride*, and *thyroid substance.*

Paroxysmal Auricular Tachycardia.—The term "paroxysmal auricular tachycardia" is a label for one of the most common varieties of disordered heart action. It is perhaps more frequent than the other types seen in patients who do

not appear to have any heart disease. It is, as the name states, paroxysmal in its behavior; it comes and goes. The duration of the attacks is extremely variable, from a series of 15 or 20 beats which produce the most fleeting commotion in the patient's chest or throat, to a paroxysm lasting many hours or even days.

In an attack, the pulse rate suddenly rises from the normal of about 70, to 150 or 200 a minute; the rhythm is regular. It rarely shows conspicuous changes in the rate with respiration or with effort, although some fluctuations in rate are occasionally seen.

Often these attacks are quite harmless. The patient walks about and continues on with his work, even though he is aware of the extreme palpitation. One of our patients is a street car conductor who continues doing his work during paroxysms, the rate of which reaches 250 a minute. Not so long ago I encountered a young woman who was able to walk about wheeling her baby carriage during paroxysms in which the heart rate was nearly 200 a minute. In her case the rapid rhythm resulted in such small stroke volume that the larger vessels began to behave like capillaries, as the result of which there was no pulse perceptible at the radial artery, and the blood pressure, which before the attack was normal, could not be recorded. It was a weird experience. We are not accustomed to seeing young patients who have become pulseless and whose systolic pressure has nearly reached the diastolic level walking about the streets. We usually associate such a condition with shock, but she clearly wasn't in shock, and as a matter of fact seemed to feel relatively few symptoms—some shortness of breath and fatigue—with this marked disturbance in the mechanics of the circulation.

Sometimes these paroxysms lead to disaster. In patients with *advanced* heart disease, the attack often precipitates heart failure and pulmonary edema.

The *mechanism* of the attack of paroxysmal auricular tachycardia is that of a series of rapid, intermittent discharges from an abnormal focus in the auricle, similar to a series of premature auricular contractions. Clinically these cases are quite indistinguishable from attacks of auricular flutter and ventricular tachycardia.

Treatment.—In about half of the cases of paroxysmal auricular tachycardia, the attack can be terminated without the use of any drugs. It is one of the most dramatic experiences in therapeutics to come upon a patient who is breathless, with marked palpitation and extreme apprehension, and by one stroke of the hand, as if by magic, the whole picture changes. The rapid rate of about 200 a minute falls abruptly to the normal of about 70, and very promptly the symptoms of distress disappear. That one stroke of the hand was the *carotid sinus pressure.*

If carotid pressure fails, use the other methods which we have described for increasing vagal activity: ocular pressure and respiratory exercises. The increased vagal tone completely suppresses the rhythmic activity of the abnormal focus in the auricle, allowing the normal pace-maker to drive the heart at the normal rate.

If these measures fail, there are other ways in which one can more effectively stimulate the vagus mechanism, namely, by the use of *emetics.* Syrup of ipecac in a dose of a teaspoonful or two will often terminate an attack which is resistant to the mechanical means of increasing vagal activity. Within ten or fifteen minutes, the patient shows severe nausea. During this period, although more often during the period of vomiting which follows, the strong vagal stimulation occurs and the tachycardia comes abruptly to an end. Apomorphine, $\frac{1}{20}$ grain by subcutaneous injection, will not infrequently accomplish the same result.

If these measures also fail, there is still another procedure which is likely to prove successful, namely, the injection of *mecholyl.* The use of mecholyl is based on the fact that when the vagus is stimulated, the effects that follow are really the result of the liberation of a charge of acetylcholine at its terminations in the heart. It is this acetylcholine which paralyzes the abnormal focus driving the heart. We first try to increase the discharge of acetylcholine by various mechanical means such as we have discussed. We appear to get an even greater discharge of acetylcholine by the use of an emetic which stimulates the vagus. But when neither of these calls forth enough acetylcholine, we make an injection of a compound which is chemically closely allied to acetylcholine and which exerts the

same kind of action upon the heart. This compound is mecholyl, or acetyl-beta-methyl-choline.

Mecholyl is provided in the form of the hydrochloride as a powder in a sealed ampoule. The usual ampoule contains 25 mg. This is dissolved in 0.5 cc. or so of water and injected subcutaneously. In extremely resistant cases, we sometimes give it intramuscularly, which accelerates its absorption. Although it is absorbed by mouth, it is much less effective that way and we rarely use it in that way. *It should never be injected intravenously because of its extreme toxicity.* One can add to its action by massaging the area of injection vigorously. Sometimes its action can be promoted by carotid sinus pressure applied from time to time during the absorption of the mecholyl. The effect of this is analogous to giving more mecholyl by injection. The disappearance of the tachycardia should take place within five to fifteen minutes after the injection. If it fails by then, give a second injection of the same size and perhaps even a third at fifteen-minute intervals. In more resistant cases, I have given as high as 60 mg. at one time by intramuscular injection with successful results.

Mecholyl stimulates all the parasympathetic structures and, before the therapeutic result is achieved, the patient may complain of apprehension, sweating, nausea, vomiting, abdominal cramps and diarrhea. If these symptoms become too distressing, they can be quickly overcome by an intramuscular injection of $\frac{1}{100}$ grain of *atropine sulfate*. A syringe containing this dose should be ready at hand before the mecholyl is given, because the toxic effects of mecholyl come on with such rapidity and vigor that considerable distress is apt to be present before there is time to prepare for the antidote.

In view of the fact that mecholyl is a parasympathetic stimulant, there is *danger* in its use in certain types of individuals who are especially sensitive to parasympathetic drugs. In patients with a history of *bronchial asthma*, a dose of mecholyl may precipitate a severe attack of bronchial asthma. In patients with *coronary disease*, the mecholyl may precipitate severe precordial pain, a source of considerable danger. As is well known, the constrictor fibers of the coronary arteries belong to the vagal system.

Our practice is to use mecholyl when other measures have

failed, because it is practically impossible to abolish paroxysmal auricular tachycardia by means of mecholyl without a considerable number of distressing side effects. The non-toxic doses are usually ineffectual and the truly effectual doses practically always produce toxic effects. The hazard, however, is greatly reduced by suitable preparation for the rapid introduction of the antidote, *atropine*.

Quinidine is also effective in the treatment of paroxysmal auricular tachycardia, but not nearly as effective as the other measures we have suggested. Large doses are apt to be necessary; doses of the order of 10 grains of quinidine sulfate by mouth every two hours until a total of 30, 40, or 50 grains has been given. These sometimes disturb the vision and the hearing and cause gastro-intestinal upsets. Even such doses are often ineffectual. An intravenous injection of 0.5 gm. of quinine dihydrochloride in about 20 cc. of fluid is sometimes more effectual. But the cinchona alkaloids are on the whole rather dangerous by intravenous injection, and unless one has had considerable experience with them, I would suggest that one avoid the use of these compounds by the intravenous route.

So far we have considered the methods which can abolish a paroxysm of auricular tachycardia relatively promptly. Sometimes all of these methods will fail. In such cases, *digitalis* may be tried. It is often quite effective. The only trouble about it is that the effects are delayed and it may take as long as ten to twelve hours to abolish an attack by means of the digitalis bodies. Such slow action, which is in the nature of the action of the digitalis bodies, has made it difficult to be certain that it ever does abolish an attack. But the evidence relating particularly to the prevention of recurrences of attacks is supported by experiences which cannot be dismissed. The dose of digitalis has to be large. On the average, a single dose of 15 grains, or about 10 cat units, may be given at one time to the average adult. This may be followed by about 6 grains, or 4 cat units, at intervals of six hours until the paroxysm disappears.

For the most part we have been considering the question of how to abolish a paroxysm of auricular tachycardia. The patient presents another problem, namely, how to prevent the *recurrence* of these attacks. As far as specific drugs are con-

cerned, only two are useful for that purpose. One is digitalis. The patient should be fully digitalized in the manner that I have just suggested, and then maintained with a daily maintenance dose varying between 2 and 3 cat units (3 to 4½ grains) daily. In this way the attacks may be completely abolished, or at any rate greatly reduced in frequency. I would suggest that this method be tried first as the most effectual method for rendering a patient free of attacks. If that proves not to be sufficient in a given case, allow several days to pass for the partial elimination of the digitalis and then turn to quinidine. Give doses of 5 grains of quinidine sulfate in tablets or capsules three times daily and increase the dosage by 5 grains daily as the need indicates until the patient is free of attacks. Some years ago we showed, in a patient in whom we were able to induce attacks of auricular tachycardia by means of epinephrine, that while quinidine failed to abolish an attack after it had been induced by epinephrine, it was, however, impossible to induce an attack when the patient was under the influence of large doses of quinidine. Quinidine, therefore, served to prevent the attacks, although it was ineffectual in abolishing any given paroxysm in this case.

You will note that practically all the major drugs used in the treatment of disorders of rhythm are at one time or another, and in one case or another, useful in the management of paroxysmal auricular tachycardia. With the proper use of these agents, rare indeed will be the case of paroxysmal auricular tachycardia which cannot be helped.

In connection with the matter of preventing the recurrence of attacks of paroxysmal auricular tachycardia, a word should be said about *causative factors,* since an effort should be made to control those factors directly, namely, hypertension, active rheumatic carditis, heart failure. In the vast majority of cases, however, we have found it almost impossible to put our finger upon the immediate causative agent. General nervousness and fatigue, mental and physical, appear to play a rôle. Patients subjected to these attacks will suffer from them much more frequently during periods of emotional tension and fatigue. It is difficult to be certain whether smoking has any particular influence upon them. Large doses of barbituric acid compounds are known experimentally to inhibit the production

of ectopic rhythms. The use, therefore, of the barbiturates in moderate doses, such as ¼ to ½ grain of phenobarbital three times daily, may occasionally influence favorably the course of an episode in which the patient is having frequent attacks. The thyroid plays an important part. Occasionally these attacks appear in patients showing an elevated basal metabolic rate, but some of the severest cases that I have seen have occurred in hypothyroid patients, patients with a metabolic rate of —25 per cent. In one young patient with such a low basal rate, severe paroxysms disappeared after sufficient thyroid material had been given to restore the metabolic rate to normal levels.

Paroxysmal Auricular Flutter.—Perhaps this is enough for paroxysmal auricular tachycardia. One important condition with which this may be confused is paroxysmal auricular flutter. Clinically, these two conditions are often indistinguishable. In both, the patient presents a rapid heart rate and in both it is usually regular, and the rates are approximately similar. The physiologic mechanism of auricular flutter is, however, quite different. In this condition there is, according to the best evidence, a circus movement circulating in a ring of muscle between the superior and the inferior vena cava, going as a rule at a rate of about 350 a minute, fatiguing the conduction between the auricle and the ventricle so that the ventricle is driven only about half that rate, namely, about 175 a minute.

Treatment.—Its response to treatment is totally different. The vagal reflex test produces temporary disturbances in the rhythm but never terminates it, as in the condition we have just discussed. The emetics and mecholyl are of no value in auricular flutter. Only two drugs can be counted upon to bring this abnormal rhythm to an end. When they are effective, the circus movement in the auricle completely disappears so that the heart is again driven by the normal sinus pacemaker. The two drugs are *quinidine* and *digitalis*. Large doses of quinidine are usually necessary, 10 grains of quinidine sulfate by mouth every two hours until such total amounts as 30 to 50 grains have been given. This drug so lengthens the refractory time of the muscle that the circus movement can no longer continue.

If quinidine is ineffectual, we may try digitalis in large doses such as I have described in connection with the treatment of paroxysmal auricular tachycardia. To one or the other of these two drugs, a paroxysm of auricular flutter does not often fail to yield.

In the absence of contraindications, I prefer to try quinidine first because, if toxic effects of quinidine are reached and the attack of flutter still continues, we can start to digitalize within twenty-four hours after the last dose of quinidine because the major part of the quinidine is so rapidly eliminated. If we start digitalis first and are unsuccessful, we may have to wait three or four days for significant elimination of the digitalis. Large doses of quinidine and digitalis sometimes act synergistically to produce toxic rhythms and it is wise to avoid the use of large doses of either of these drugs when the patient is still under the influence of a large dose of the other.

Only one specific drug has been found capable of preventing the *recurrences* of attacks of auricular flutter: That drug is quinidine. The procedure in regard to dosage for the prevention of attacks is to start with 5 grains of quinidine sulfate by mouth three times daily and, if attacks recur on this dose level, to increase the dose by 5 grains daily until a daily dosage level is reached which is effectual in preventing the recurrence of attacks. Such a procedure is very safe even though the dose level which proves effectual may be as high as 40 or 50 grains daily. Sometimes such dose levels cannot be reached because toxic symptoms prevent it. This procedure is valuable only in those cases in which attacks are fairly frequent and disturbing. If they recur only at intervals of a few months, it is perhaps in general more satisfactory to treat the individual attack than to continue large doses of quinidine to prevent the attack which comes at such infrequent intervals.

Paroxysmal Auricular Fibrillation.—The mechanism in the heart which produces auricular fibrillation is similar to that of auricular flutter. It is a circus movement, but of a more complex nature, circulating through the walls of the auricles, maintaining the auricles in a state of diastole, while the walls seem to quiver. There is only one specific agent which has the power to abolish this mechanism in the auricle, namely, *quinidine*. What one says about quinidine, of course, applies

also to the other cinchona alkaloids. Quinine is also effective, although somewhat less so.

One usually thinks of *digitalis* in connection with auricular fibrillation, but while digitalis is the drug of choice in the average case of persistent auricular fibrillation in order to maintain a slow heart rate, digitalis does not abolish the fibrillation in the auricles. Quinidine, as I have stated, is the only drug capable of doing this.

The doses necessary for the abolition of an attack of auricular fibrillation, as well as for the prevention of the recurrence of attacks, must be established in each case individually, and the general plan suggested under the treatment of auricular flutter will apply to this condition as well.

Emphasis should be placed upon the fact that the abolition of auricular fibrillation by quinidine has very limited application. Most cases of auricular fibrillation do as well, if not better, if they are allowed to continue to fibrillate and the ventricular rate is slowed by digitalis. *Quinidine should not be employed* if there is enough disease to cause heart failure, if the abnormal rhythm has persisted for months, if the heart is inordinately large, in cases of advanced mitral stenosis, or in any cases in which there is reason to suspect that thrombus formation may exist in the auricle. The classical indications are those cases without valvular lesions or without any organic heart disease, in which the fibrillation recurs in paroxysms and in which the attack has not persisted longer than a week or two.

Ventricular Tachycardia.—The counterpart of paroxysmal auricular tachycardia occurring in the ventricle is ventricular tachycardia. This name, like auricular tachycardia, labels a rapid series of intermittent discharges originating in the ventricles. They are similar to a series of ventricular extrasystoles. The rate may vary from 100 or so to 200 or 250 a minute. The condition is less common than auricular tachycardia. It is more often associated with grave myocardial disease.

Unlike paroxysmal auricular tachycardia, there is only one drug which can abolish it, namely, *quinidine*. Digitalis may make the condition worse. In any case, it cannot abolish it. Large doses of quinidine are usually necessary. The procedure which we usually follow is to give 10 grains of quinidine

sulfate by mouth every two hours.   At times the condition
seems so desperate, especially when occurring in a patient
with an acute coronary thrombosis in whom a ventricular rate
of 200 a minute is seriously impairing the circulation, that we
proceed with even larger doses, 15 grains every two hours un-
til total doses as high as 60 to 70 grains have been given.   That
the drug is proving effective may be observed by the gradual
slowing of the idioventricular rhythm until the abnormal
rhythm is completely abolished and the sinus rhythm takes
its place.   In the more resistant cases requiring large doses,
frequent electrocardiograms taken during the treatment help
to avoid overdosage—which may produce dangerous prolonga-
tion of intraventricular conduction.

Heart Block.—I may add a very few words about the
treatment of heart block.   Most cases of complete heart block
require no treatment at all.   They carry on fairly well with
the slow ventricular rate of 30 or 40 a minute, and if signs
of failure develop, they are digitalized in the usual manner.
There are two types, however, in which patients with heart
block suffer attacks of syncope, or Adam-Stokes attacks.   The
treatment of these two types is different.   In one, the attacks
of syncope occur when the heart passes from partial A-V block
to complete A-V block, or even in the reverse direction.   The
object of the treatment is to prevent this shift.   In many
cases it can be accomplished by giving large doses of *digitalis*
such as I have already discussed.   These will induce more or
less permanent, complete A-V block, and in this state the pa-
tient usually carries on quite satisfactorily.

In the second variety, the syncopal attacks occur in a
patient who already has a complete A-V block, but the
rhythmic activity of the ventricle is so bad that the rate may
suddenly decline from 30 or 40 to 9 or 10 a minute.   These
fluctuations in the idioventricular rhythm are sometimes influ-
enced by drugs which increase the rhythmic activity of the
ventricles.   *Ephedrine* is sometimes useful in these cases, in
doses as large as the patient can tolerate, starting with ½ grain
of ephedrine sulfate three times daily.   *Barium chloride* some-
times produces effectual increase in the rhythmic activity of the
ventricles.   It may be given in doses of ½ to 5 grains three
times daily in a teaspoonful of water.   The syncopal attacks
due to this second variety of heart block are very resistant to

treatment and therapeutic failures in this group are quite common.

Comment and Summary.—In closing, I may direct attention to two matters: The first is the fact that in the treatment of rapid abnormal rhythms the primary aim is to slow the rapid heart rate, but the traditional view as to how this may be brought about, namely, by the slowing of a rapid pacemaker, does not apply. It is very difficult to slow the speed of a rapid pace-maker in the human heart by the direct action of drugs. Indeed, it is impossible to produce lasting slowing by such means. It is nevertheless a fact that in cases of sudden tachycardia with a rate of 200 a minute or faster, persistent slowing at a rate of 70 or 80 a minute does result from a few doses of quinidine or digitalis. There is no conflict in these facts if one bears in mind that while it is difficult to maintain the slowing of a pace-maker in the heart, it is quite easy to suppress an abnormal pace-maker completely, and thereby allow a slower pace-maker elsewhere in the heart to control the beat. This is the way cardiac slowing takes place in the paroxysmal disorders of rhythm by means of the drugs which we have mentioned.

Secondly, while a sudden paroxysm of rapid heart action is in some cases the only cardiac problem, in others it may be the result of a serious cardiovascular disorder. For example, an attack of auricular flutter may produce symptoms as well as changes in the electrocardiogram that are strongly suggestive of an acute coronary closure, both of which disappear promptly with the restoration of the normal rhythm, the subsequent examination of the patient revealing no evidence of organic heart disease. On the other hand, an attack of auricular flutter or fibrillation may be precipitated by the development of rheumatic "activity" in the myocardium or by an acute coronary thrombosis without intense pain or marked reduction of the blood pressure. These may escape detection unless there is careful searching. In a discussion such as this, in which the center of interest is the abnormal rhythm, it may be well to lay emphasis on this matter, for an acute disorder of rhythm is often the heart's most dramatic performance and is likely to engage attention to the exclusion of other factors, having in some cases equal if not greater significance.

CLINIC OF DR. NORMAN TREVES

MEMORIAL HOSPITAL

RECENT THERAPEUTIC MEASURES TO CONTROL PAIN IN CASES OF INCURABLE CANCER

THE last decade has seen an enormous improvement in caring for the incurable cancer patient. The relief and comfort which can be afforded him is often quite striking, rendering a cancer death no more terrifying and at times even less appalling than the last days of a patient suffering from pulmonary, cardiac, or renal disease. Since most of the real progress in cancer therapy has been made in recent years, let us not look upon it as a sad picture, but rather as a splendid and intelligent attack upon an implacable enemy of the human race.

Narcotics vs. Mild Hypnotics and Sedatives.—Many practitioners feel that the easiest way to treat the patient suffering from incurable cancer is to employ large doses of *narcotics* indiscriminately. The psychology for such dosage is: the end is inevitable and if the patient is continuously narcotized, he is comfortable and the anxiety of the relatives is relieved. This attitude is deplorable. One cannot tell how long the terminal phase may last. If it drags on the opiate will have to be increased, so that huge amounts will finally have to be administered. At times the employment of such large amounts of narcotics becomes necessary and in such instances they should not be withheld.

Mild hypnotics and *sedatives* should first be employed in minimal doses, the amount being increased when necessary. Among these drugs are the newer barbiturates and barbituric acid derivatives. *Phenobarbital, sodium amytal, pentobarbital sodium* (nembutal) and *seconal* are some of the newer hypnotics which are most satisfactory. The depressing action which followed the prolonged administration of the older hyp-

notics is less frequently observed with these newer drugs. *Aspirin* or *phenacetin* with caffeine may be combined for analgesic effect. When this form of medication is no longer effectual, then one may use *codeine*, or combine codeine with them. Finally, the *opium* derivatives will have to be employed.

As an advance in opiate medication, dihydromorphinone hydrochloride (*dilaudid*) has been introduced. Dilaudid has been employed in place of morphine because of certain distinct advantages it possesses. It has been said to be a stronger analgesic, requiring a dose one-fifth that of morphine; it acts more quickly and is less likely to produce undesirable side effects; and it is better tolerated, producing a more effective analgesia. In therapeutic doses it has very little hypnotic action and does not affect intestinal peristalsis. When pain is to be relieved and sleep induced, some barbituric acid derivative must be combined. Dilaudid, unlike morphine, has very little effect on the gastro-intestinal tract and rarely is responsible for nausea, vomiting, or constipation. Early cancer pain can often be relieved by a capsule containing $\frac{1}{48}$ grain of dilaudid and 10 grains of aspirin. A solution of 1 grain of dilaudid in 6 ounces of peptenzyme elixir provides an economical and flexible solution for oral administration, the dose being 1 or 2 teaspoonsful. Although dilaudid is most frequently given hypodermically in doses of $\frac{1}{32}$ or $\frac{1}{20}$ grain, $\frac{1}{24}$ grain oral tablets or rectal suppositories containing $\frac{1}{24}$ grain are often used when hypodermics are inconvenient or undesirable or when the speed of action is not essential. Even in these dosages, however, dilaudid must be used with the same caution as other opiates.

Neither a patient nor a patient's relatives should judge the *quantity* of an analgesic or narcotic, nor the *time interval* which should elapse between doses. Smaller amounts will be needed and the time interval lengthened if the medicine is given under close supervision.

In malignant inoperable or recurrent growths, the alleviation of pain is often the main objective of the physician. In certain instances pain may appear at a late stage in the disease and persist until death but may be controlled with even the simplest analgesics. However, in many cases pain is intense and persistent, particularly in the late stages of disease, so that even alkaloids are completely ineffective or effective

only for a short space of time. For this reason a continuous search has been going on for medicines which would be capable of eliminating the excruciating pain for prolonged periods.

Intravenous Alcohol Infusions.—As early as 1927 Thurz investigated the influence of intravenous ethyl alcohol infusions upon the pain produced by inoperable malignant neoplasms. He recorded the prolonged analgesic effect following such therapeusis. The method has been used for recurrent and metastatic melanoma, mammary carcinoma, ovarian cancer and carcinoma of the vagina.

Thurz is unable to account for the analgesic effect of the alcohol. He feels that the action is two-fold: The first action is directly upon the nervous system, and the second upon the growth itself. He states that, experimentally, the growth regresses in size following the intravenous administration of the alcohol; as a result, pressure on adjacent tissues, especially nerves, is reduced.

Careful blood and urine analyses before and during this type of medication showed no changes. There was no evidence of renal damage and the blood picture was unchanged.

Technic.—For the infusions a 33 per cent ethyl alcohol solution (1 part absolute ethyl alcohol and 2 parts physiologic saline solution) is used. The *initial dose* is 1 cc. of alcohol for each kilogram of body weight. Thus a patient weighing 50 kg. (121 lbs.) would receive 150 cc. of the solution intravenously. The medication is administered through the usual infusion set with glass trap and the *rate of drip* is between 30 and 40 drops per minute. The needle should contain physiologic saline solution at the time it is introduced into the vein and the alcoholic solution washed out of the needle before withdrawal. If this precaution is not observed, pain is experienced and skin damage occurs. As soon as the alcohol is introduced the patient experiences transient pain along the course of the vein. This soon disappears. If the alcohol is administered at a rate exceeding 60 drops a minute there is loss of consciousness.

The alcohol is given *every third day* and the amount of solution increased until 450 to 600 cc. are given at one treatment.

Response to Treatment.—The response following this

treatment varies: Some patients become drowsy immediately and enjoy an undisturbed sleep often lasting six hours. Others become noisy, laughing or crying, and exhibit all the symptoms of an alcoholic delirium which ends in somnolence. They awake refreshed and show no ill effects from the therapy. Analgesia may be noted following the first treatment. The intravenous infusion of 33 per cent ethyl alcohol seems to be an entirely harmless procedure.

Thurz reported his results in the treatment of ten patients: All seem to be benefited. I have tried it upon eight patients, with relief in six cases and no relief in two.

Calcium Therapy.—In 1933 Shear reported the effects which followed the administration of large doses of calcium in metastatic carcinoma of bone and, in the same year, Behan independently advanced the reasons for the relief of pain in cancer by calcium. Brunschwig in 1935 reported two striking results following its use. Both patients had extensive metastases to the bony pelves and suffered extreme pain on locomotion. Ten per cent calcium gluconate was given intravenously in a dose of 10 cc. three times a day for one month and 10 gm. of calcium gluconate were given three times a day by mouth. After the continued calcium medication roentgenograms demonstrated increased density in the destructive bone areas. The pain and discomfort were so remarkably relieved that both patients were able to perform moderate work and exercise.

In the writer's experience, medication with calcium must be continued *indefinitely*. At times, even more striking results are obtained with calcium therapy where it is combined with the administration of *vitamins* (A and D) and minute doses of *thyroid extract*. The diets of patients with incurable cancer are vitamin deficient for several reasons: The amount of food taken is small. Besides, the diet is frequently liquid in character and lacks balance. This lack of vitamins A and D will affect bone and, if such vitamins are present in insufficient amounts in the diet, calcium metabolism will be deranged. These vitamins may be supplied by using cod liver or halibut liver oil, plain or irradiated. A very satisfactory product containing all three is *Calcium A*, made by Ayerst, McKenna and Harrison.

Behan's hypotheses advanced in his report are quite inter-

esting and his conclusions are based on an interesting review of the literature. He states that the reduction in the pain reaction of patients with cancer who are treated with calcium may also, in part, be hypothesized upon: (1) changes in the irritability of the nerves in the cancer area; (2) changes in the conductivity of the nerves from the cancer area to the brain, and (3) a decreased activity of the pain perception centers in the brain.

A change in calcium metabolism is also produced by *ultraviolet irradiation*. The increase of the serum calcium in the blood following exposure to ultraviolet rays may explain the beneficial effect of this type of irradiation on pain.

Parathyroid gland extract will also increase the calcium content of the blood and at the same time decrease the electrical excitability of nerve tissue. However, since this medication increases serum calcium at the expense of the calcium present in the bones, it may provoke metastasis to bone deprived of its normal calcium content. Hence it does seem wise to combine parathyroid extract with the administration of large amounts of calcium.

Cobra Venom.—Cobra venom was first scientifically employed at the Pasteur Institute where it was found useful in relieving the severe pains accompanying malignant disease. While the work of these investigators has been reported by Macht as being favorable, Lavedan, at the Radium Institute in Paris, using cobra venom in fifty-one cases of cancer, obtained only insignificant analgesic effects and noted no influence whatever on the growths themselves. This is at variance with the results not only of Macht, but recently with those of Rutherford. The latter's results, however, appear to be unusually good and do not coincide with the other reports in the literature and with the writer's experience utilizing cobra venom.

Both laboratory and clinical results show that *moderate doses* (5 to 10 mouse units) do not injure either the circulation, the kidney, or liver function: "Pharmacologic studies on the drug reveal that its toxicity is not as great as compared with its therapeutic efficiency; in other words, the margin of safety is wide and the therapeutic index is a high one."

Macht, in his pharmacologic investigations, established that

the minute quantities of cobra venom employed therapeutically in dilute concentrations produce no demonstrable local anesthetic action either on the sensory or motor nerve endings or the nerve fibers of the ascending or descending peripheral nerves. On the contrary, all the experiments point to the pain areas in the cerebrum as the points of analgesia produced by the injection of cobra venom. The conclusion drawn was that cobra venom, like morphine, relieves pain by its action on the higher centers of the brain. The marked difference in the two drugs was that morphine relieved pain promptly but lost its effect in a few hours. Cobra venom induces analgesia more slowly, requiring several days of successive hypodermics. When the analgesia is induced it lasts much longer.

The *usual dose* of cobra venom is 5 mouse units. (A mouse unit is the quantity of cobra venom solution required to kill a white mouse weighing 22 gm. within eighteen hours after the intraperitoneal injection of the drug.) However, it is safer to use *only half* the contents of an ampule: 2½ mouse units (ampules manufactured by Hynson, Westcott and Dunning). On the following day the entire content of an ampule—1 cc.— is administered. Similar doses are injected on successive days until a definite analgesia is noted. No unfavorable sequelae have been noted. Thereafter two or three injections a week may be utilized to keep the patient comfortable. Such therapy may be continued for months. The hypodermics should be given *intramuscularly*.

Macht reports definite relief in 70 per cent of the cases he treated (185). Rutherford reports complete relief of pain in 46 per cent of the patients he treated with cobra venom. The writer has used it in a dozen cases with noticeable relief in all but one.

Very often cobra venom has been used as a last resort when all other therapeutic measures have failed. It was gratifying to find that in many instances analgesics and narcotics were gradually reduced and finally omitted after the cobra venom had been given for sufficient lengths of time to become effective. Some observers have noted an improvement in their patients' mental attitude. Whether this is a true euphoria from the drug or merely the result of relief from pain and improvement in the general condition cannot be determined.

Vitamin Therapy.—The use of vitamins in general practice is rapidly increasing. While it may be premature to accept in entirety the claims made for their administration, we have been impressed with the favorable results. In treating patients with incurable cancer, vitamin B_1 and C, as well as A and D, have a definite sphere for their use. It is within the scope of this résumé to mention briefly the uses of vitamin B_1.

Vitamin B_1.—The diets of patients with incurable cancer are vitamin deficient for several reasons: the food intake is often limited; the diet is frequently liquid in character; and lastly, it lacks balance. Vitamin B_1, the "antineuritic vitamin," has a wide usefulness in its relation to nutrition and health. Anorexia is often the initial symptom of dietary vitamin B_1 deficiency. Many of the neuritides, as well as neuroses, may result from such an avitaminosis. Nerve pain, local or generalized, is often complained of. The areas affected may contain neither metastases nor extensions of the disease. In the absence of definite evidence of physical involvement, one may suppose the neuritis might be caused by a vitamin deficiency. The administration of vitamin B_1 may ameliorate these symptoms. The general improvement which often follows its use may lead to increased resistance to pain.

Vitamin B_1 (synthetic vitamin B_1, known as *"Thiamin Chloride"—Betaxin, Betabion, Berocca*) is available in crystalline and tablet form. *Parenterally* the dose is 25 mg. daily, though it is now thought that doses over 10 mg. are excreted in the urine unchanged. Tablets from 1 to 10 mg. are available for oral use. At least 3000 International Units should be administered daily.

While it has not yet had a fair chance to show its worth, the B complex gives promise of even increased value in treating the neuritides in advanced cancer. Certainly it improves the general condition of the patient. *B complex* (Lederle) is available for oral or intramuscular use.

The use of these substances will not replace analgesics and hypnotics, but their administration often lessens the amounts of such drugs that are used to control pain.

Comment and Summary.—Now that so many drugs are available for relieving pain, no patient should reach the stage when he desires an operation in the hope that it may lead to

death; nor should he be allowed to linger on in agony with his pain unrelieved. Unfortunately, it is still difficult when life may likely last for many months to counteract pain at all times; for if drugs are administered over a long period, they may eventually fail to act or may lead to demoralization which ultimately may be as distressing to the patient and his family as severe pain.

We must hope that the future will provide many new drugs and methods for the relief of pain in cases of incurable cancer —ones even more helpful than those which have recently been made available.

BIBLIOGRAPHY

Behan, R. J.: Reasons for the Relief of Pain in Cancer by Calcium. Am. J. Surg., 19: 301–306, 1933.

Brunschwig, A.: Observations on the Administration of Large Doses of Calcium in Metastatic Carcinoma of Bone. Am. J. Cancer, 25: 721–729, 1935.

Lavedan, J.: Le Traitement des Tumeurs Malignes de l'Homme par le Venin de Cobra. Bull. de l'Acad. Méd., 113: 195–207, 1935.

Macht, D. I.: Therapeutic Experiences with Cobra Venom. Ann. Int. Med., II, 1824–1833, 1938.

Rutherford, R. N.: The Use of Cobra Venom in the Relief of Intractable Pain. New Eng. J. Med., 221: 408–413, 1939.

Shear, M. J.: The Rôle of Sodium, Potassium, Calcium and Magnesium in Cancer: A Review. Am. J. Cancer, 13: 924–1024, 1933.

Thurz, D.: Über Schmerzsbillende Wirkung intravenoser Alkoholinfusionem bei Krebskranken. Wien. klin. Wchnschr., 51: 691–692, 1938.

CLINIC OF DR. JANET TRAVELL

DEPARTMENT OF PHARMACOLOGY, CORNELL UNIVERSITY
MEDICAL COLLEGE

SOME RECENT ADVANCES IN HYPNOSIS AND SEDATION

AT the outset of this discussion it should be stressed that in all insomnias and other states of increased functional activity of the nervous system, the primary objective is the *determination of the cause*. Sometimes the cause is obvious, such as pain or cough, and an effective mode of therapy self evident. On the other hand, even when the cause is known, it may be impossible to remove it, and symptomatic treatment by central depressant drugs must be employed. Usually the cause is quite obscure, and insomnia or nervousness is described as "idiopathic." In the last group treatment cannot be so readily directed toward removal of the cause, but the search for effective modes of therapy continues and often affords a clue to the etiology. In some instances successful treatment by the psychiatrist indicates that emotional factors were responsible for the nervous imbalance, or relief of symptoms by suitable sex hormone therapy places it on a menopausal basis. More recently a new avenue of therapeutic approach has been opened up by the discovery that nutritional deficiencies may play a causal rôle. The recognition of this fact means that a number of insomnias and other functional nervous disorders may be shifted from the category referred to as "idiopathic" to the category of known etiology, but how large will be the proportion of cases transferable in this way is entirely speculative at the present time.

NUTRITIONAL FACTORS AS HYPNOTICS AND SEDATIVES

Vitamin B_1.—Among the nutritional factors, attention was first directed toward Vitamin B_1 as a sedative and hypnotic in toxic alcoholic states, in which the relation of a deficiency

of this vitamin to the production of polyneuritis was already
well known. Brodsky[1] observed that the chronic alcoholic psy-
choses of thirty-six patients were cured by the administration
of Vitamin B_1 when a daily dose of only 500 to 2000 units
(1.5 to 6 mg.) was injected intramuscularly for a period of
several weeks. Kloster[2] was enthusiastic about the effect on
impending delirium tremens of the intravenous injection of a
50 mg. dose of crystalline Vitamin B_1, after which improve-
ment was apparent within an hour or so. In the majority of
the ten patients treated in this way, normal sleep was ob-
tained on the first night and no further administration of the
vitamin was necessary. Karnosh[3] has confirmed these findings
in nine cases of fully developed alcoholic delirium, but found
it necessary to administer thiamin chloride intravenously in
somewhat larger dosage, 50 mg. on each of three or four suc-
cessive days. Under this plan of treatment, all of the symp-
toms of confusion disappeared and normal sleep was restored
within five or six days.

The suggestion[3] that Vitamin B_1 may act as a sedative and
hypnotic in other toxic states, such as thyrotoxicosis, still lacks
convincing proof.

Vitamin C.—Vitamin C also has been reported as pos-
sessing a hypnotic action. When the effects of large doses of
ascorbic acid were studied in sixty patients with insomnia
(twenty sane and forty insane), it was found[4] that 1 gm. daily
of levo-cevitamic acid given by mouth induced sound sleep
within three days in all the sane, and within seven days in
thirty of the insane patients. Some of the remaining insane
patients responded to larger doses. The hypnotic effect usually
persisted for only twenty-four hours after discontinuing the
medication. No evidence was presented to show that a de-
ficiency of this vitamin existed. The results of this study
would be more convincing if the conclusions were based, at
least in the case of the sane group, on objective measurements
of the duration and depth of sleep instead of on a subjective
appraisal, and if some of the patients had received a placebo
to serve as control for the psychologic effect of medication
under the conditions of the experiment.

That a deficiency of Vitamin C may exist in toxic and ex-
haustive states has been demonstrated by numerous studies

showing a reduction in the Vitamin C concentration in the blood or in the amount excreted in the urine, in thyrotoxicosis, in alcoholic addiction, and in senile and other types of psychoses. Wortis and his collaborators[5] have shown, furthermore, that the concentration of Vitamin C is subnormal in the blood and spinal fluid in patients with alcoholic delirium, but not in alcoholic addicts without neurologic or mental changes. It is not unlikely that Vitamin C, as well as Vitamin B_1, may prove an effective sedative and hypnotic under these circumstances, but it is not clear how ascorbic acid might exert a hypnotic effect in conditions in which there is no apparent deficiency of this vitamin. It is, however, at the present time impossible to define what constitutes a normal supply of the vitamins for the various tissues of the body, and the Vitamin C content of the brain is known to vary widely at different ages and in its different portions. It has been conjectured that massive doses of Vitamin C, such as were given by Maurer, even in the apparently normal individual, may increase the available supply of the vitamin to those areas which are most susceptible to its deprivation, smaller doses being relatively ineffective for this purpose.

Nicotinic Acid.—There is evidence that other nutritional factors may act as sedatives and hypnotics when the symptoms are due to specific deficiencies of these factors. The rapidly curative effect of nicotinic acid on the acute psychoses of frank pellagrins and on the "neuroses" (insomnia, unrest and anxiety, distractibility, forgetfulness, and palpitation) of mild or subclinical pellagrins has been amply demonstrated.[6] In these cases, a total of 0.5 to 1.0 gm. of nicotinic acid by mouth daily in divided doses caused the disappearance of the mental and nervous symptoms in from one to twelve days, whereas Vitamin B_1 was without influence on them. Furthermore, nicotinic acid had no hypnotic or sedative effect in the acute psychoses of a group of patients lacking evidences of a deficiency of this factor.

In toxic alcoholic states, nutritional deficiencies may be multiple. A case of delirium tremens has been reported[7] in which hypnosis and sedation followed the administration of nicotinic acid, after two doses of thiamin chloride had failed to influence the confusion and excitement, and in which there

were some evidences of a deficiency of nicotinic acid. Unfortunately, it is not certain in this case whether a delayed response to Vitamin B_1 was observed, or whether the effects were due to nicotinic acid alone, or to a combined action of both essential factors.

BARBITURIC ACID DERIVATIVES

Foremost in popularity among the compounds used to induce sleep and sedation directly are the barbituric acid derivatives which are now enjoying a vogue almost to the exclusion of all others. Sales of the barbiturates in the United States in 1936 amounted to the staggering figure of more than 174,000 pounds, which would represent over 2,200,000 average therapeutic doses (1½ grains) per day.[8] Blind adherence to new fashions in hypnotics, the mere addition of new barbiturates to the already long list, and the indiscriminate use of these substances by the medical profession itself, which often overshadows the need for discovering the basic causes of the symptoms, cannot be considered advances in therapy.

On the other hand, intensive investigation has yielded many significant pharmacologic facts about the barbiturates which should serve as the basis for rational therapy. A fundamental contribution toward the demonstration of these facts was the development by Koppanyi and his collaborators[9, 10] of satisfactory chemical tests for the barbiturates and of methods for their extraction. Suggestions have recently been made by the laboratory of the Mayo Clinic for some useful modifications of these methods, in particular as to the extraction of the new, unstable short-acting barbiturates from blood and tissues.[11]

The large mass of experimental data on the barbiturates deals almost entirely with the effects of these drugs in relation to anesthesia: their seat of action, margin of safety, speed of onset and duration of effects, distribution and elimination, and toxic actions on the heart and circulation, liver, kidneys, and other systems of the body. Although it is true that this material serves as the background for our knowledge of their sedative and hypnotic actions, the conclusions based on experiments employing anesthetic doses in either animals or humans should not be transferred directly to the special problems involved in the use of these agents for hypnosis and sedation.

Toxicity.—Recent studies have added little that is new to our fundamental knowledge of this aspect of the subject, especially as to toxicity in humans. For example, in the case of the blood and blood-forming organs, an anesthetic dose of pentothal sodium, the newest member of the barbiturate family to appear in the limelight, has been found[12] to produce in dogs essentially the same effects as had been reported for other barbiturates, that is, as much as a 20 per cent reduction in the red cell and hemoglobin values, probably as the result of the storage of blood in the enormously dilated spleen. Carraway[13] reports that, clinically, sodium pentothal anesthesia is nontoxic to the blood as shown by a comparison of the post-operative and preoperative values for hemoglobin, red and white cell counts, and bleeding and coagulation times. The reported anemia-producing property of evipal has been reinvestigated,[14] and anemia was not observed in healthy dogs anesthetized with evipal as many as twenty-two times in five months. Clear-cut evidence is lacking to incriminate the barbiturates, especially those which do not contain the benzene ring, as acutely toxic for the blood. The evidence is fragmentary, however, and systematic investigation, both clinical and pharmacologic, is needed to determine the effects of the long-continued use of hypnotic doses of the barbituric acid derivatives on the blood directly and on the response of the blood to extraordinary conditions, such as dietary deficiencies, infection, and the use of other drugs and toxic agents.

An important alteration in the response of the cortical and medullary centers to the barbiturates is suggested by experiments on rats previously treated with large doses of *sulfanilamide*.[15] For all of the barbiturates studied (evipal, pentothal, amytal, nembutal, thioethamyl) it was found that after sulfanilamide subanesthetic doses became anesthetic and sometimes fatal, whereas ordinary anesthetic doses proved fatal in a large proportion of the animals. There was practically no difference in the toxicity of either tribromethanol (avertin) or of the volatile anesthetics in the sulfanilamide-treated and untreated animals. It is obvious that investigation of the reported synergism of the barbiturates with sulfanilamide should be extended to include both hypnotic and anesthetic doses in other species of animals and in man.

The barbiturates in hypnotic doses have been shown to be a potential source of poisoning in the *nursing infant*. Tyson and his collaborators have directed attention to the fact that phenobarbital, in a daily dose of from 1½ to 2 grains[16] as well as other hypnotic and sedative agents such as the bromides,[17] when administered to the lactating mother may be excreted in the breast milk in amounts sufficient in some instances to produce effects in the nursling.

Duration of Hypnotic Action.—Since the introduction of the rapidly excreted barbiturates about nine years ago, it has gradually come to be accepted that those members of the group possessing a short duration of anesthetic action, even evipal, may be successfully used in the treatment of insomnia. This general impression has not been subjected to critical investigation and, on the face of it, seems rather illogical, except possibly in the case of those patients with insomnia who experience difficulty only in falling asleep.

In this connection the carefully controlled experiments carried out by Dr. Lawrence W. Hanlon at the Willard State Hospital, New York, are of interest.[18] The effects of the ordinary maximum hypnotic dose of sodium barbital (10 grains) and of sodium pentobarbital* (3 grains), and those of a placebo, were compared in each of sixteen psychiatric patients with marked insomnia. Observations as to whether the patient was awake or asleep were made at frequent stated intervals during the night, after each of the above medications and also in initial and terminal control periods without any medication. The total number of nights of observation was 450, or an average of 28.1 per patient. Marked relief of sleeplessness was obtained in fourteen cases, and in these the hypnotic effects were as striking after the rapidly excreted as after the slowly excreted barbiturate. This applied not only to insomnias which had been present early in the night, but also to those insomnias which had persisted through the latter part of the night, corresponding to the period of from five to eight and one-half hours after administration of the drugs. The reasons for this finding are not clear at the present time, but several explanations suggest themselves: One possibility is that the doses of pentobarbital and barbital employed (ratio of

* Nembutal.

1:3.3) might not be found comparable in terms of the minimal effective hypnotic dose of each, were this known, and that the dose of pentobarbital may have been relatively greater. Another possible explanation is that the abolition of the insomnia in the latter part of the night is not due to a direct action of the drug at all, but rather to other factors affecting the mechanisms of sleep, such as the early relief of fatigue and increased muscular relaxation.

There is need for the application of objective laboratory methods to clinical comparisons of the hypnotic effects of the various barbiturates with each other and also with the older centrally depressant drugs which have fallen somewhat into disuse. A recent study[19] has made such a comparison of the effects of several barbiturates and a placebo on the onset and duration of sleep, and on the gross movements, blood pressure, respiratory and pulse rates during sleep, in essentially normal patients. No significant differences in these phenomena were observed, probably owing to the fact that the subjects did not have insomnia. Were such technics applied to the action of these drugs in persistent psychogenic insomnia, it seems certain that significant contributions would be made to the mechanisms of action of hypnotic agents and to rational therapeutics in this field.

Dosage for Hypnosis.—One of the principles which becomes apparent from the use of the so-called "short-acting" barbiturates for hypnosis is that the more rapid the rate of excretion or destruction, the smaller the ratio of the intravenous anesthetic dose to the oral hypnotic dose. This point may be illustrated as follows: For *evipal*, which is eliminated almost as rapidly as it is absorbed from the gastro-intestinal tract, the oral hypnotic dose approaches the intravenous anesthetic dose; thus, 8 grains of evipal by mouth may be required to induce sleep, and only one and one-half times this amount, 12 grains, required by vein to induce narcosis. For *amytal*, which is much more slowly eliminated, the intravenous anesthetic dose (about 40 grains) is thirteen times the maximum recommended oral hypnotic dose (3 grains); and for *pentobarbital*, which is intermediate between evipal and amytal in its rate of disappearance from the body, the former (about 20 grains) is seven times the latter (3 grains).

Mathematical formulas·for the rate of detoxification of the barbiturates have been derived, when the speed of elimination is measured by a form of biologic titration; that is, by the amount of the drug required to·cause death when injected intravenously at a standard rate at varying intervals after the previous administration of the barbiturate.[20]   This method is analogous to the intravenous titration with ouabain to determine the amount of a digitalis glucoside acting in the body at a given time.   It was shown in this way that ninety minutes after the intravenous injection of a nearly fatal dose of nembutal in rabbits, practically all of this dose had been eliminated from the body.   This is of interest in connection with the hypnotic effect of relatively small doses of this barbiturate in man, which we have shown may persist for as long as eight hours.

BIBLIOGRAPHY

1. Brodsky, M. E.: Treatment of Alcoholic Psychoses with Thiamin Chloride. J. Conn. Med. Soc., 2: 228, May, 1938.

2. Kloster, J.: B₁-Vitaminbehandlung bei Delirium Tremens. Nervenarzt, 11: 413, August, 1938.

3. Karnosh, L. J.: The Treatment of Insomnia. J.A.M.A., 113: 1322, Sept., 1939.

4. Maurer, S., Wiles, H. O., Schoeffel, E. W., and Fisher, M. L.: Effect of l-Cevitamic Acid in Insomnia: Preliminary Report. Ill. Med. J., 74: 971, July, 1938.

5. Bowman, K. M., Wortis, H., and Keiser, S.: The Treatment of Delirium Tremens. J.A.M.A., 112: 1217, April, 1939.

6. Speis, T. D., Aring, C. D., Gelperin, J., and Bean, W. B.: The Mental Symptoms of Pellagra: Their Relief with Nicotinic Acid. Am. J. Med. Sci., 196: 461, Oct., 1938.

7. Mainzer, F., and Krauss, M.: Nicotinic Acid in the Treatment of Delirium Tremens. Brit. Med. J., 2: 331, August, 1939.

8. Hambourger, W. E.: A Study of the Promiscuous Use of the Barbiturates. Their Use in Suicides. (Report of the Council on Pharmacy and Chemistry.) J.A.M.A., 112: 1340, April, 1939.

9. Koppanyi, T., Murphy, W. S., and Krop, S.: Studies on Barbiturates. Arch. Internat. de Pharm. et de Thérap., 46: 76, 1933.

10. Koppanyi, T., Dille, J. M., Murphy, W. S., and Krop, S : Studies on Barbiturates. II. Contributions to Methods of Barbital Research. J. Am. Pharm. A., 23: 1074, 1934.

11. Delmonico, E. J.: Tests for Derivatives of Barbituric Acid. Proc. Staff Meetings Mayo Clinic, 14: 109, Feb., 1939.

12. Searles, P. W.: The Effect of Certain Anesthetics on the Blood J.A.M.A., 113: 906, Sept., 1939.

13. Carraway, B. M.: Pentothal Sodium with Nasal Oxygen: A Report of 3,810 Consecutive Cases. Anesth. and Analg., **18**: 259, Sept.–Oct., 1939.

14. Beecher, H. K.: On the Reported Anemia-Producing Qualities of 1-methyl-5-Δ'-cyclohexenyl-5-methyl-barbituric acid (Evipan, Evipal). J. Pharmacol. and Exper. Therap., **63**: 335, July, 1938.

15. Adriani, J.: Effects of Anesthetic Drugs upon Rats Treated with Sulfanilamide. J. Lab. and Clin. Med., **24**: 1066, July, 1939.

16. Tyson, R. M., Shrader, E. A., and Perlman, H. H.: Drugs Transmitted Through Breast Milk. II. Barbiturates. J. Pediat., **13**: 86, July, 1938.

17. Tyson, R. M., Shrader, E. A., and Perlman, H. H.: Drugs Transmitted Through Breast Milk. III. Bromides. J. Pediat., **13**: 91, July, 1938.

18. Hanlon, L. W., and Travell, J.: A Clinical Study of a Rapidly Excreted and a Slowly Excreted Barbiturate in Insomnia. Unpublished.

19. Meyers, F., Cook, E., and Page, R. C.: A Clinical Study of Hypnotics. N. Y. State J. Med., **40**: 12, Jan., 1940.

20. Kohn-Richards, R., and Grimes, C.: Detoxification of Barbiturates and the Influence of the Method of Administration: Demonstrated with Nembutal and Pentothal. Anesth. and Analg., **18**: 139, May–June, 1939.
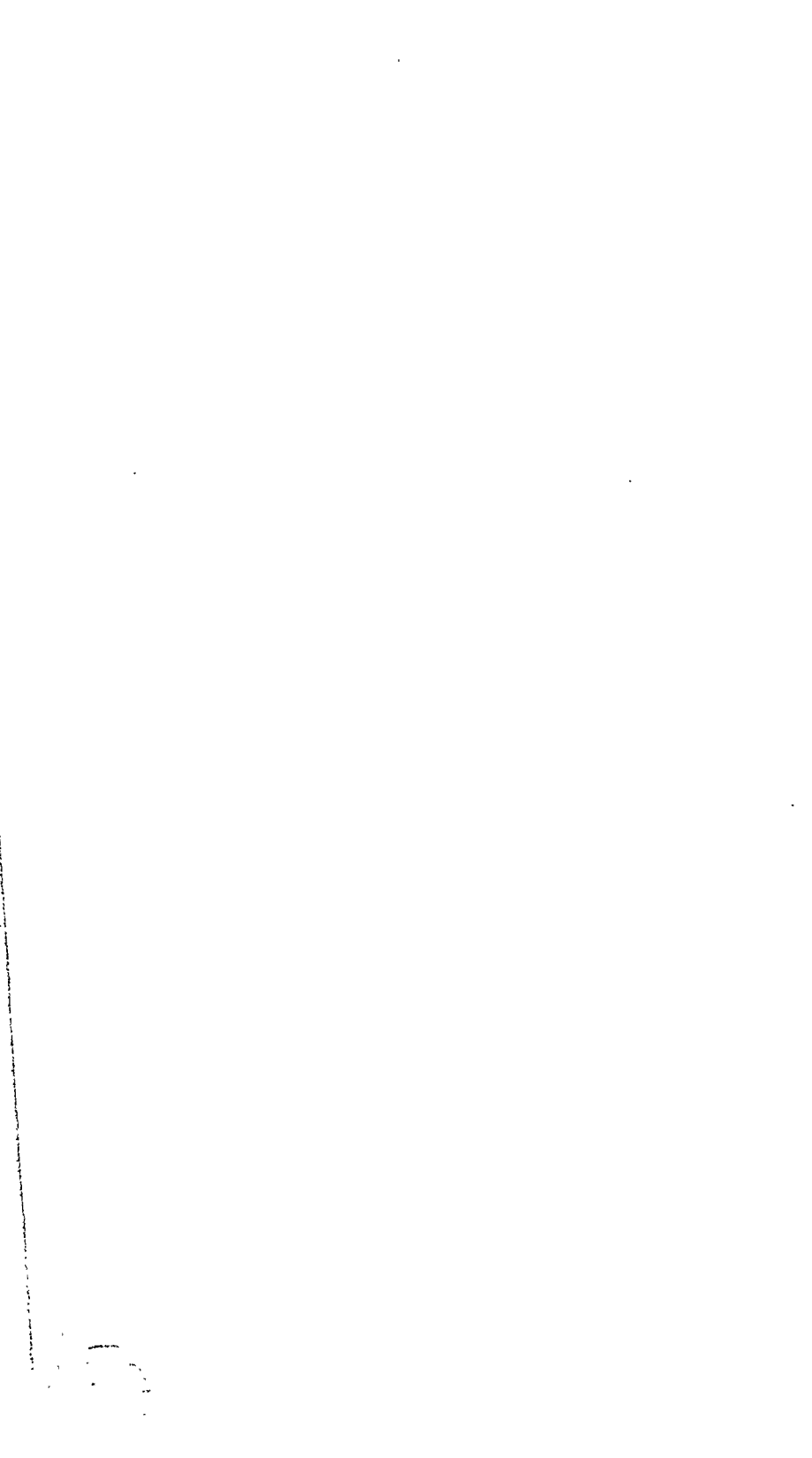
CLINIC OF DR. VIRGINIA APGAR

PRESBYTERIAN HOSPITAL

RECENT ADVANCES IN ANESTHESIA IN GENERAL
· PRACTICE

MANY of the recent advances in anesthesia seem to be available only to the larger hospitals, either because of complex apparatus needed, or because of the need of a well-trained medical specialist in anesthesia. It is a pleasure, therefore, to note some of the advances made in anesthetic drugs and technics which can be used in general practice.

Even more important than advance in drugs and technics is the advance in anesthesia instruction, especially in the past five years. Except in urban localities, the majority of anesthesias are and will continue to be administered by the general practitioner. Frequently the newly-graduated physician meets the subject of anesthesia abruptly during the first weeks of his practice when he is faced with a can of ether, a gauze-covered mask and a patient. His instruction is supplied by the surgeon, whose attention is diverted from the operative field by problems arising at the head of the table. At best this is a poor system of training. Any physician may be called upon to administer anesthetic agents and it is his right to learn the principles of anesthesia before he leaves medical school. This is being recognized by schools throughout the country in a gratifyingly quick fashion. Qualified medical specialists in anesthesia, interested in teaching, are supplying theoretical and practical instruction to undergraduate students in about thirty-four of the sixty-eight four-year medical schools. The quality of training in anesthesia during internship is improving, and the number of residencies in the subject has increased twentyfold in recent years. Anesthesiology will undoubtedly be a most rapidly growing specialty during the next ten years.

Inhalation Technics and Drugs.—Three fundamental principles guide the choice of drugs and technics in general practice: *dependability, simplicity* and *portability*. Portable anesthesia machines, using small tanks of compressed gases with to-and-fro carbon dioxide absorption units, are now made by several companies. This equipment will bring to many small hospitals anesthesia produced by a variety of gases, such as *nitrous oxide, ethylene* and *cyclopropane*. However, the equipment should be accompanied by a physician trained in the use of such gases. In the rapidity of action of the above gases lies their *ease* of control, but also the *danger* in their use. Accidental severe states of anoxia or overdose of drug are much more frequent than with the more irritating volatile agents.

The most dependable, simple and portable method of anesthesia is still the time-worn *open-drop ether anesthesia*. Though the mask and drug have remained the same for many years, advances have been made in the administration of the drug which bring it up in importance to a newly discovered drug. The use of *premedication*, such as morphine and scopolamine in individualized dosage, has facilitated induction, depressed the amount of mucous secretion, and lessened the amount of ether needed for tissue saturation. The recognition of the need for an *unobstructed airway* throughout anesthesia has diminished the number and severity of postoperative pulmonary complications. The appreciation of the metabolic dangers of *anoxemia* has led to the use of a thinner covering for the mask, and the discontinuance of towels except during induction. A quick recovery and return of the protective cough reflex is obtained by utilizing the knowledge of *planes of anesthesia*, as described by Guedel in his book, "Fundamentals of Inhalation Anesthesia." *Postoperative nausea* and *emesis* are lessened by the use of adequate fluids, glucose, protein and vitamin therapy preoperatively. The incidence of *atelectasis* and *pneumonia* has been lowered by maintaining a good minute volume exchange postoperatively, by conservative use of morphine for pain relief, frequent change in position of the patient, and encouragement of hyperventilation.

Other volatile agents are available for anesthesias of short duration requiring little relaxation. *Ethyl chloride* dropped

slowly on a thin mask will suffice for a myringotomy, or shorten an ether induction, but the danger of myocardial damage is ever present. *Chloroform*, the only nonexplosive hydrocarbon in use, is useful when cautery around the head and neck is to be used, but appreciable *liver damage* accompanies any chloroform anesthesia, however short. *Vinethene* affords a quick, pleasant induction and recovery, but certain adverse experimental results remain to be explained satisfactorily.

Regional Anesthesia Technics.—In general practice, regional technics have a particularly important place. All minor surgery and much major work may be accomplished with the help of *block* anesthesia. Any practitioner may become proficient in these technics, after careful review of anatomy, aided by some reference book such as Labat's "Regional Anesthesia," and a moderate amount of practice.

For *circumscribed superficial lesions,* a rectagonal field block is adequate. *Rectal work* lends itself to perianal infiltration, caudal or transsacral block. In *obstetrics*, a caudal block greatly facilitates the second stage of labor, and episiotomy repair can be performed with this anesthesia or with infiltration of the vaginal walls. *Fractures* or *lacerations* below the elbow are rendered painless with a brachial block; the *hematoma* at any fracture site can be aspirated and the area filled with an anesthetic solution, with resultant relaxation of muscle spasm, and a painless reduction. Operations in the *inguinal region* lend themselves to an abdominal wall field block, as do most *emergency* operations in the abdomen itself. However, if much manipulation of intestines is needed, a *spinal* anesthesia will be more satisfactory. This type of block involves additional risk because of its relative uncontrollability, and a competent observer must be available to manage any complications which may arise. *Surgery of the thyroid* can be performed with bilateral cervical plexus block. A paravertebral anesthesia is useful in *rib resections*, or in relieving pain in cases of fractured rib, with a surprising decrease in the incidence of accompanying pulmonary infection.

Of the drugs available for block anesthesia, *procaine* (novocaine, neocaine) is still the most dependable and the least toxic. It is important to remember that its toxicity increases in geometric proportions. One cubic centimeter of 1 per cent

solution is four times as toxic as the same amount of 0.5 per cent solution. If a solution as strong as 2 per cent is used, *only 30 cc.* can be safely employed. The *larger* the amount of solution that is needed, the *weaker* its strength should be. Great care, by repeated aspiration, must be taken to prevent *intravenous* injection of the drug.

A valuable contribution to block anesthesia was the discovery by Tatum and his coworkers that preanesthetic barbiturates protect to a large degree against the convulsive action of this group of drugs. The short acting barbiturates are the most reliable, such as *nembutal* or *seconal,* given orally one hour before anesthesia. Intravenous barbiturates likewise will stop a convulsion produced by procaine. They do not protect, however, against the occasional circulatory depression. Ephedrine, paredrine, or neosynephrin may be used to treat this condition.

Intravenous Technics and Drugs.—The simplicity of the intravenous technic and the portability of the drugs used for this type of anesthesia at first glance make this method seem most desirable for use in general practice. For minor procedures, its quick induction and quick recovery are most desirable.

The use of intravenous anesthesia is *absolutely contraindicated,* however, unless one physician is available *solely to attend to the anesthesia and its complications.* Many times it has proved fatal to the patient for the surgeon to administer a fixed dose and then proceed with the operation. The most important immediate complications occur in *the respiratory* system, either *respiratory depression* from overdosage of the drug, or *respiratory obstruction* from relaxation of the tongue, or laryngospasm.

These complications must be treated immediately. The administration of the drug is stopped, a free airway is obtained either with a pharyngeal tube or intratracheal tube, and oxygen is administered. The most available source of oxygen is the physician's exhaled air.

The numerous *respiratory* and *circulatory stimulants* on the market are attractive in theory, but practically in such markedly depressed patients, excessive doses are needed, and

the stimulant action, if obtained, is short-lived. The immediate need is to get *oxygen* to the patient's tissues.

Two barbiturates, *evipal* or *pentothal*, are the commonly used agents.

Rectal Technics and Agents.—There is no satisfactory total anesthetic agent which may be administered by the rectal route. *Ether in oil* is sometimes used for surgical operations, but if ether is the drug chosen, the inhalation route affords much more accurate dosage and control. *Tribrom* or *trichlorethanol* have a place in medication, but *only if excellent nursing care is available postoperatively*. The late return of the cough reflex and the prolonged period of metabolic depression add considerably to the risk of this drug.

Treatment of Intractable Pain.—The general practitioner can contribute much to the comfort of his patients who are suffering from severe pain if he will consider anesthetizing the sensory nerves involved. Many patients with *carcinoma* are able to lead a useful life if only their pain is relieved. Opiates are of course effective, but usually remove the patient from an active sphere of usefulness. Pain arising from lesions in the spinal cord or brain itself is not amenable to block therapy. Other conditions in which this type of treatment is to be considered are *herpes zoster*, painful *arthritis*, and *phantom limb*. The pain of *angina pectoris* has often been removed by nerve block, but with the loss of this symptom, angina patients more frequently become decompensated from exceeding their exercise tolerance.

The drug usually used for these blocks is *absolute alcohol*, preceded by a local anesthetic such as *procaine*. The treatment is not wholly without complications, for paresthesias may exist for several days, varying amounts of muscular paresis may result (which is usually temporary), and loss of sphincter control occurs after a small per cent of blocks involving the lumbosacral region. The region remains anesthetic for three or four months, when the block can be repeated. The patient should be advised before the block that the painful area will not feel normal but "wooden." Some patients object to this almost as much as to the pain.

The *site of the injection* should be determined by the loca-

tion of the smallest nerve fibers supplying the region. Alcohol is much more regular in its action if *small* nerves are blocked rather than larger trunks. In a painful arm from metastatic carcinoma, a brachial block will be less satisfactory than a low cervical paravertebral block. Occasionally, in the lumbar region, the drug may be introduced intrathecally, especially if the paravertebral block has not been satisfactory.

It is possible that some of the new drugs in oily solutions, such as *eucupin, butycaine,* or *neothesol,* which have been almost uniformly successful in rectal operations, will be adapted to nerve block technics, for anesthesia of seven to ten days' duration.

A new substance has been made available recently for treating intractable pain from any cause: *Cobra venom,* administered intramuscularly, has produced considerable relief. Three hundred cases have been treated so far in this country, with about 70 per cent success. Its action is not fully understood, but seems to be central rather than peripheral. The drug is slow to reach its maximum action, and is excreted slowly, with the result that one dose may suffice for two or three days in an average case. One ampule, or 5 mouse units, is given daily until some analgesic effect is noted. Thereafter, 1 ampule at intervals of two to three days or longer is needed to maintain the analgesia. So far no adverse effects of the drug have been observed. Other sedatives may be greatly diminished in dosage, or even omitted. Cobra venom has also been substituted for morphine in confirmed addicts without any withdrawal symptoms. The drug is still in the experimental stage, but the possibility of self-administration and the apparent absence of contraindications and toxic reactions suggest that it will have a permanent place in the therapeusis of pain.

Miscellaneous Block Therapy.—Impetus to the use of nerve blocks for various conditions was given by several surgeons in France, Germany and Italy. Among other uses are the treatment of *phlebitis* by a sympathetic chain block, described further in this country by Ochsner; stellate ganglion block for *asthma;* thoracic or lumbar sympathetic block for *angiospastic diseases of the extremities.* Diagnostically, the presence of a hyperactive *carotid sinus reflex* may be proved

by blocking the reflex with procaine at the site of the bifurcation of the carotid artery into its external and internal branches. Many fields remain to be explored both diagnostically and therapeutically.

Resuscitation.—There are about 50,000 asphyxial deaths a year. Almost all of these are seen first by the *general practitioner*, and the initial attempts at resuscitation are performed by him. In spite of the large number of mechanical devices on the market to maintain respiration, none is more available than the *physician's own expired air.* The pressure with which it is delivered is individually regulated, whether it be for a newborn infant, or for an adult; the mixture contains ample oxygen, about 14 per cent, and 4 per cent carbon dioxide.

No method of resuscitation, however, whether it be Schaefer, Nielsen, or a Drinker respirator, is effective unless a free airway is present. Obviously this means *removal of mucus, vomitus, water* or other fluids from the tracheobronchial tree, by use of the *head-down position* and by *suction* if that is immediately available. The usual barrier to resuscitation is at the larynx, because of the highly irritable vocal cords which adduct into a *laryngospasm.* This can be relieved by passing a tube between the cords, thus preventing their spasm and supplying a free airway.

An *endotracheal tube* and *laryngoscope* should be part of every physician's equipment. Frequently the tube can be passed blindly through the nose without visualizing the cords or opening the mouth. In some schools, fourth year medical students and interns are being taught this simple and necessary technic.

It is beyond the scope of this review to discuss the *detailed technics* of the methods described above. For this reason, a few references are appended which will give this information:

BIBLIOGRAPHY

Alexander, F. A. D., and Cullen, Stuart: Preanesthetic Medication. Am. Jour. Surgery, 34: 429–434, 1936.

Guedel, A. E.: Fundamentals of Inhalation Anesthesia. The Macmillan Co., 1937.

Labat, Gaston: Regional Anesthesia, 2nd Ed. W. B. Saunders Co., 1928.

Macht, D. I.: Therapeutic Experiences with Cobra Venom. Annals Int. Med.. 11: 1824–1833, 1938.

Ochsner, A.: Treatment of Thrombophlebitis by Novocain Block of Sympathetics. Surgery, 5: 491–497, 1939.

Pamphlet No. 3; Exhibit on Anesthesia, under the Auspices of the American Medical Association, 1939.

CLINIC OF DRS. ALVAN L. BARACH AND HENRY A. CROMWELL

DEPARTMENT OF MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE PRESBYTERIAN HOSPITAL

RECENT ADVANCES IN OXYGEN AND HELIUM THERAPY, WITH SPECIAL REFERENCE TO THE TREATMENT OF BRONCHIAL ASTHMA

Historical Background.—In a discussion òf recent advances in inhalation therapy, it seems fitting to call attention to the fact that modern oxygen therapy began with the physiologic studies of Haldane and Barcroft, who not only demonstrated the harmful effects of oxygen-want in human subjects, but also made clinical application of oxygen-enriched atmospheres. Haldane[1] employed a face mask to treat the irritant pulmonary edema caused by phosgene, and Barcroft[2,3] constructed the first oxygen chamber to administer oxygen in late cases of war gas poisoning. The beneficial results which they reported stimulated clinical studies abroad and in this country.

Hürter,[4] who demonstrated the safety of the arterial puncture, had already reported blood gas studies; he used the technical methods of Haldane and Barcroft, which showed that a decreased oxygen content in relation to the oxygen capacity occurred in certain cases of *pneumonia*. Stadie[5] confirmed and amplified these findings in a larger series of cases, and found that the degree of cyanosis in pneumonia was proportional to the degree of arterial oxygen unsaturation. He constructed an oxygen chamber with a motor-driven system of ventilation like that of Barcroft, and treated patients with pneumonia with oxygen-enriched atmospheres. The inhalation of 40 to 60 per cent oxygen was found to elevate the oxygen saturation of the arterial blood to or near the normal

value in many cases of pneumonia by Stadie,[5] Meakins,[6] and Barach[7]; the two latter workers used simpler methods than the oxygen chamber. It was also found that the arterial and venous oxygen saturation in *congestive heart failure* could be regularly increased by inhalation of from 40 to 60 per cent oxygen.[7]

Leonard Hill[8] reported the use of an oxygen bed tent in the case of a soldier who had had his femoral artery tied and who suffered from *chronic ulcers* of the extremity. Within forty-eight hours healing of the ulcers had begun in a remarkable way. This case stimulated additional research on methods of oxygen therapy which were both effective and comfortable. Since Leonard Hill's tent had no cooling or dehumidifying device, attempts were made to improve his apparatus,[9, 10] and finally the method of circulating the oxygen-enriched atmosphere directly over chunks of ice was found to provide a hygienic atmosphere in respect to temperature and humidity.[11]

The *ventilated* oxygen tent has come into practical use as the most comfortable of the readily available effective methods of providing oxygen. A *portable* oxygen chamber was also developed, using the same method of ventilation,[12] and a simpler type of oxygen chamber or oxygen room which employed thermal circulation of the contained atmosphere.[13] The advantage of ventilating an oxygen room by exposure of the atmosphere to cold pipes on one side and a steam radiator on the other is its freedom from motors, electricity, fans and all source of sparks.

The *nasal catheter* was originally introduced in England by Stokes and Ryle,[14] then came into general use in this country as the simplest method of continuously administering oxygen.[15] Higher concentrations were obtained from its use when it was placed in the oral pharynx opposite the uvula (Waters and Wineland[16]).

Oxygen Therapy in Pneumonia and Cardiac Disease. —As a result of the employment of these various methods, the value of oxygen therapy in *pneumonia* was additionally studied. It appeared that there was a proportional relation between severe anoxemia and mortality[5, 17, 18]; there was suggestive evidence that oxygen treatment had a favorable effect

on mortality rate[19, 20]; it was demonstrated that oxygen therapy in certain cases did not only promote the comfort of the patient but was life-sustaining[21]; and in postoperative pneumonia, oxygen therapy was shown to have a specially favorable influence, and often had a specific effect in the lowering of temperature.[22, 23]

Among the later uses of oxygen therapy was its effect in restoring compensation in cases of *congestive heart failure,* especially those in which the cause was arteriosclerotic heart disease[24] and early rheumatic heart disease.[25] The crucial importance of oxygen therapy in *acute coronary occlusion* was clearly shown in carefully studied cases.[26] More recently, the use of oxygen in the treatment of *pulmonary emphysema* and *pulmonary fibrosis* has shown that dyspnea may be relieved and life prolonged by the judicious use of oxygen treatment over long periods of time.[27, 28, 29, 30]

High Concentrations of Oxygen.—The proposal that *very high concentrations* of oxygen, 95 to 100 per cent, be used in the treatment of pneumonia and cardiac disease originated with Evans,[31] who reported that the clinical symptoms of anoxemia were often not relieved until these high concentrations were employed. It appeared that animals did not die when exposed to 100 per cent oxygen for sixteen hours a day,[32] although continuous use of this concentration for over two days has long been known to cause irritant changes in the lungs of animals, with death in from five to seven days. However, harmful effects have not been noted in human subjects exposed to 95 per cent oxygen for two days and even longer. Fine and his associates[33] have shown that inhalation of pure oxygen will remove accumulated nitrogen from the body cavities or tissues in a comparatively short time, and they have used the method for treatment of intractable *abdominal distention.* In cases of *headache after encephalography,* the inhalation of 100 per cent oxygen will either greatly reduce or clear up completely all discomfort in a period of one-half to four hours after treatment is begun.[34] Boothby *et al.*[34] reported the administration of 90 to 100 per cent oxygen to 100 patients for one to four days, with intermissions of a few minutes every three to four hours, without signs of pulmonary irritation in any case. The increased amount of oxygen in

physical solution is the main physiologic advantage of giving 90 to 100 per cent oxygen. In conditions of *severe anoxemia,* such as peripheral circulatory failure, acute coronary occlusion, acute pulmonary insufficiency in emphysema, tetanus, and pulmonary edema, these high concentrations may be useful for a period preferably not exceeding forty-eight hours. The administration of 100 per cent oxygen has been advocated for the treatment of *migraine*[35] and *seasickness.*[34] If given early in the attack of migraine, some cases appear to be benefited by this procedure.

Oxygen Therapy in Pulmonary Edema and Bronchial Obstruction.—Oxygen has been administered in conjunction with positive pressure for the treatment of pulmonary edema and bronchial obstruction; the results obtained from the application of positive pressure are summarized by Barach *et al.*[36]

Acute pulmonary edema may arise as a result of left ventricular failure, with a backing up of blood in the lungs and an increased hydrostatic pressure in the pulmonary capillaries; it may arise as a result of increased capillary permeability due to inflammation, anoxemia, or irritation, such as in pneumonia or war gas poisoning. Pulmonary edema may also occur as a symptom of shock.

The time allotted to this presentation does not permit an evaluation of all the mechanisms involved, but we wish to point out that the breathing of oxygen (or air) under a *positive pressure* of 3 to 6 cm. of water has been employed to retard the entrance of blood into the right heart and the lungs, thereby diminishing pulmonary congestion and to exert an opposing pressure on the external capillary wall, which tends to retard exudation of serum. Clinical use of this procedure has resulted in the clearing of pulmonary edema in cases of pneumonia and cardiac disease. It is best applied with the helium-oxygen hood, but simpler methods, such as an anesthesia mask or exhaling against 5 or 6 cm. of water, have been used.[36] Breathing against positive pressure has also been used to prevent exudation of serum and mucus following *tracheotomy.*[37, 38] Finally, it has been shown that breathing under positive pressure maintains a larger bronchial lumen during expiration in cases of *bronchial asthma,* studied by lipiodol roentgenograms in patients breathing oxygen with and without

positive pressure.[39]   The application of positive pressure is, however, *contraindicated* in shock—in which there is already a difficulty in the return of venous blood to the right heart.

Helium-Oxygen Therapy in Bronchial Asthma.—The use of helium as a method of providing oxygen to the lung at a lower pulmonary pressure has been described in cases of severe bronchial asthma and obstructive lesions of the tracheo-bronchial tree.[40]   Owing to the low specific gravity of helium, a mixture of 20 per cent oxygen 80 per cent helium passes through constricted orifices at a pressure approximately one-half that required for pure oxygen or air.   In *status asthmaticus,* the inhalation of 25 to 35 per cent oxygen, with the remainder helium, has been found effective when other measures have failed, and at times has proved a life-saving remedy.[41, 42, 43]

Obstructive lesions in the upper respiratory passageway may occur as a result of infection, pressure, or laryngeal spasm; the inhalation of helium-oxygen mixtures may allow respiration to continue with diminished effort until the original cause of obstruction has been removed.   Its advantages in *anesthesia* have been described by Eversole[44] and others.[45]

Treatment.—During the remainder of this lecture we wish to present a program for the treatment of severe bronchial asthma which utilizes intermittent inhalation of helium-oxygen mixtures.

There is a large group of patients with bronchial asthma who take repeated injections of adrenalin daily, or who use at frequent intervals some form of adrenalin by spray.   In these cases, the relief obtained from adrenalin becomes transitory and incomplete.   In some instances the condition increases in severity to the point of status asthmaticus.   In the majority, a state of severe asthma may persist for long periods, varying somewhat from day to day.   Physiologic studies on these patients reveal that some degree of acute functional emphysema exists and that a pathologically elevated negative intrapleural pressure is present during the inspiratory cycle.[40, 41]   The inhalation of helium-oxygen mixtures reduces the negative pressure necessary for the act of inspiration; this effect is increased if the gas is inhaled under positive pressure.   In addition, the smallness of the helium molecule makes possible its entrance

and exit from hitherto unventilated or poorly ventilated portions of the lung, and results in more efficient emptying of the lung, decreasing progressively the pulmonary distention.

In a previous communication by the senior author,[26] fifty-four cases of asthma of various types were described, in ninety per cent of which a specifically beneficial effect could be ascribed to helium-oxygen therapy which was characterized by disappearance of the severe asthmatic state. The benefit from intermittent inhalation of helium-oxygen mixtures in the treatment of bronchial asthma has been confirmed by Metz et al.[46] In a recent series of thirty cases we have used, in addition to helium-oxygen treatment, the administration of *potassium iodide* and the *intravenous* injection of *hypertonic solutions.* Potassium iodide has long been recognized as a valuable agent in the treatment of bronchial asthma. In the Handbook of Therapy, edited by Fishbein (1937) it is stated: "Perhaps the most frequently helpful drug in preventing the recurrence of asthma is an iodide, probably because most asthma is due to an involvement of the air passages, and this drug is specifically a stimulant to the mucous membrane of the nose, throat and bronchial tubes." The value of iodides has also been stressed by Boch,[47] who believes they possess a synergistic action with ephedrine sulfate. In our experience, potassium iodide appears to lessen recurrence of bronchial asthma and is of value in decreasing the state of allergy itself.

Hypertonic solutions have been administered with the purpose of decreasing edema in the bronchial and bronchiolar walls. At times the immediate effect is a noticeable decrease of dyspnea; in most instances, however, no obvious lessening of bronchial spasm is observed. From 50 to 100 cc. of 50 per cent glucose is given intravenously during a period of ten to fifteen minutes. Sucrose is to be avoided since it may be irritating to the kidneys and its administration is at times followed by reactions. In some cases, 10 per cent salt solution has been administered in doses of 50 to 100 cc. The beneficial effects of glucose injection may also be related to its effect on blood potassium. Rusk et al.[48, 49] have reported a lowering of serum potassium, accompanied by clinical improvement, following injection of glucose in patients with bronchial asthma. The mechanisms involved in potassium metabolism are too lit-

tle understood at present to warrant extensive comment. Studies which we are conducting in collaboration with John Scudder appear to confirm the observation that the serum potassium is apt to be higher during the period of severe asthma, but there are many factors involved, such as dehydration, which need further investigation.

Technic.—The program which we have mainly used may be summarized as follows:

1. *Inhalation of helium-oxygen mixtures for one to five hours daily for five days.* If the patient is in the *hospital* and is suffering from very severe bronchial spasm, the helium-oxygen *hood* is employed, two hours in the morning, two hours in the afternoon, and one hour in the evening. A *pressure* of 2 to 3 cm. of water is generally used. The *oxygen concentration* of the mixture is 25 to 35 per cent, the higher oxygen concentration being chosen if pulmonary distention is severe. For *less severe* asthma, the B-L-B mask[31] is employed and a concentration of 20 per cent oxygen and 80 per cent helium is inhaled one hour three to five times daily. In *office practice,* the B-L-B mask is used, the helium-oxygen mixture being inhaled one hour daily, for five days.*

2. *Inhalation of vaporized 1:100 epinephrine solution.* The preparation we have found most effective is called "Vaponefrin." The nebulizer made by this company is better than

---

*In our use of the B-L-B mask in dyspneic subjects, 6 to 8 liters a minute of oxygen is inadequate to provide comfortable breathing, the subject being unable to take a deep breath without collapsing the bag. Furthermore, the CO_2 concentration in the inspired air climbs above 2 per cent in many instances at a flow of 6 liters per minute. When oxygen is used, a flow of 10 to 12 liters per minute is to be preferred for the reasons above mentioned. We have also substituted a lighter bag made of *latex* material in order to reduce the work involved in collapsing a bag of heavier material. The latex bag is somewhat larger and of an elastic quality which can be used to provide positive pressure, especially in expiration. When a helium-oxygen tank is used with an oxygen gauge, the latter may be set at 5 to 7 liters per minute. This will provide a flow approximately of 9 to 12 liters of the helium-oxygen gas.

Since this article was written we have added to the program here described the use of *aminophylli.* In severe cases this is given intravenously and intramuscularly; in patients who are ambulatory, it is given either in the office by the physician or at home by the patient as a rectal instillation of 0.48 gm. metaphylli in 50 cc. of warm tap water. For this purpose the intramuscular 2 cc. ampule is employed.

others we have tried; the solution remains in suspension in the atmosphere a longer time than 1:100 epinephrine. Before and after treatment with helium, the patient inhales from 0.25 to 0.5 cc. of Vaponefrin solution after it has been vaporized by passage of 5 liters per minute of oxygen through the nebulizer. The vapor is breathed continuously through the mouth. As the patient improves and bronchial spasm disappears, Vaponefrin or epinephrine inhalation is dispensed with except for acute attacks.

3. *Potassium iodide is given in saturated solution:* 1.0 cc. on arising, 1.0 cc. at 6 p.m., and 1.0 cc. on retiring. If the patient is awake during the night, 1 to 2 cc. additional may be taken. This is continued until the patient is free from severe asthma. The administration of KI is continued, however, 0.5 to 1.0 cc. twice daily for an indefinite period. If an iodide eruption takes place, administration of the drug is discontinued for a few days or weeks and then recommenced. If administration of potassium iodide is stopped, the patient should be cautioned to begin it as soon as symptoms of asthma begin to increase.

4. *An intravenous injection of 50 to 75 cc. of 50 per cent glucose is administered for the first two or three days of treatment.* If the patient is hospitalized and appears dehydrated, a preliminary infusion of 1000 cc. of 5 per cent glucose in saline is given.

In some cases *shortness of breath* develops following injections of glucose. Of ten patients with asthma, a reduction in vital capacity took place in all following injection of 50 to 100 cc. of 50 per cent glucose; the decrease averaged 25 per cent of the control observation, measured generally about five minutes after the injection. It seems desirable to inject the solution over a period of ten or fifteen minutes. No serious reactions were produced in any case. The period of dyspnea, when it did occur, gradually cleared up within half an hour, at which time the vital capacity had returned nearer to the control figure.

Results.—The above described program of treatment has been employed in thirty cases during the past year. In eleven, intermittent helium-oxygen treatment was used for two days

or less, in twenty-six other cases between two and five days, and in four additional cases more than five days. There was no improvement that could be specifically attributed to this program in three cases; moderate and gradual improvement took place in fifteen and marked improvement occurred in twelve. In the last mentioned group, the benefit from the program outlined was dramatic and appeared to be unmistakably the result of the specific therapy attempted. Of the total group of thirty cases, cessation of the state of severe bronchial asthma took place in twenty-seven. The duration of the state of relatively mild or no asthma varied considerably: In eight instances the improvement has now continued for two to four months; in seven cases no recurrence of severe asthma has taken place over a period of eight to twelve months; in five cases severe asthma recurred in two months or less; in seven cases of this group severe asthma recurred in three to six months.

It is beyond the province of this presentation to discuss the factors involved in recurrence of the state of severe bronchial spasm. Obviously, exposure to the offending allergic substance is an important cause. As we have intimated, the continuous administration of KI appeared to prevent recurrence of asthma in many, although not in all, cases. We wish to point out especially the effectiveness of intermittent inhalations of helium-oxygen mixtures together with the administration of potassium iodide and hypertonic solutions. In the vast majority of this recent series of cases, as well as in over 90 per cent of fifty-four patients previously reported, termination of the state of severe bronchial asthma has been accomplished by this procedure.

The details of the technic of treatment have been reported in recent communications.[45, 46] A more complete report of the clinical cases will be published subsequently.

Inhalation of 100 per cent *nitrogen* has been used in *psychotic* patients with results that appear to be comparable to those of insulin.[50] This recalls the use of CO_2 and oxygen inhalations which were first used to produce convulsions in the treatment of dementia praecox, two out of five cases of the first series obtaining remissions.[51]

BIBLIOGRAPHY

1. Haldane, J. S.: Recent Developments in the Therapeutical Use of Oxygen. Contributions to Medical and Biological Research Dedicated to Sir Wm. Osler, 1: 550, 1919; Therapeutic Administration of Oxygen. Brit. Medical Jour., 1: 181, 1917.

2. Barcroft, J.: The Respiratory Function of the Blood. The University Press, Cambridge, 1914.

3. Barcroft, J., Cook, A., Hartridge, H., Parsons, T. R. and Parsons, W.: Flow of Oxygen Through the Pulmonary Epithelium. J. Physiol., 53: 450, 1920.

4. Hürter, von: Untersuchungen am arteriellen menschlein Blute. Deutsch. Arch. f. Klin. Med., 108: 1, 1912.

5. Stadie, W. C.: The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis. J. Exper. M., 30: 215, 1919.

Stadie, W. C.: Construction of an Oxygen Chamber in the Treatment of Pneumonia. J. Exper. Med., 35: 323, 1922.

Stadie, W. C.: Treatment of Anoxemia in Pneumonia. J. Exper. Med., 35: 337, 1922.

6. Meakins, J. C.: Observations on the Gases in Human Arterial Blood in Certain Pathological Pulmonary Conditions, and Their Treatment with Oxygen. J. Path. and Bact., 24: 87, 1921.

7. Barach, A. L., and Woodwell, M. N.: Studies in Oxygen Therapy with Determinations of the Blood Gases. I. In Cardiac Insufficiency and Related Conditions. Arch. Int. Med., 28: 367, 1921; Studies in Oxygen Therapy. II. In Pneumonia and Its Complications. Arch. Int. Med., 29: 394, 1921.

8. Hill, L.: A Simple Oxygen Bed Tent and Its Use in a Case of Edema and Chronic Ulcer of the Leg. J. Physiol., 50: 1921; Proc. Physiol. Soc., p. 20.

9. Barach, A. L. and Binger, C. A. L.: A Portable Oxygen Tent. J.A.M.A., 85: 190, 1925.

10. Roth, P.: Bulletin, Battle Creek Sanit. & Hosp. Clin., 19: 178, 1924.

11. Barach, A. L.: A New Oxygen Tent. J.A.M.A., 87: 1213, 1926.

Barach, A. L.: The Importance of Ventilation in Oxygen Tent and Oxygen Chamber Therapy, with a Description of an Improved Oxygen Tent. N. Y. State J. Med., Oct. 15, 1931.

12. Barach, A. L.: An Oxygen Chamber Simplified in Design and Operation. J.A.M.A., 97: 390, 1931.

13. Barach, A. L.: A New Type of Oxygen Chamber. J. Clin. Invest., 2: No. 6, 1926.

14. Stokes and Ryle: Discussion on Therapeutic Uses of Oxygen, Proc. Roy. Soc. Med. (Sec. Therap. and Pharmacol.), 13: 59, 1920.

15. Barach, A. L.: The Administration of Oxygen by the Nasal Catheter. J.A.M.A., 93: 1550, 1929.

16. Waters, R. M. and Wineland, A. J.: Oxygen Therapy; Insufflation into Oral Pharynx. Arch. Surg., 22: 67, 1931.

17. Binger, C. A. L.: Anoxemia in Pneumonia and Its Relief by Oxygen Inhalation. J. Clin. Invest., 6: 203, 1928; Therapeutic Value of Oxygen in Pneumonia. N. Y. State J. Med., 25: 953, 1925.

18. Binger, C. A. D., Hastings, A. B., Neill, J. M. and Morgan, H. J.: Blood Reaction and Blood Gases in Pneumonia. J. Clin. Invest., 1: 25, 1924.

19. Barach, A. L.: Oxygen Therapy in Pneumonia. N. Y. State J. of Med., Aug. 15, 1929.

20. Faget, C. H. and Martin, W. B.: The Oxygen Therapy of Pneumonia. Hospital News, 4: 20, October 15, 1937.

21. Barach, A. L.: Acute Disturbance of Lung Function in Pneumonia. J.A.M.A., 89: 1865, 1927.

22. Boothby, W. M. and Haines, S. F.: Oxygen Treatment. Am. J. Surg., 7: 174, 1929; Value of Oxygen Treatment After Thyroidectomy. Am. J. Surg., 6: 1, 1929.

23. Binger, M. W., Judd, E. S., Moore, A. B. and Wilder, R. M.: Oxygen in the Treatment of Patients with Post Operative Pneumonia. Arch. Surg., 17: 1047, 1928.

24. Barach, A. L. and Richards, D. W.: Effects of Treatment with Oxygen in Cardiac Failure. Arch. Int. Med., 48: 325, 1931.

25. Poulton, E. P.: Local Tissue Anoxia and Its Treatment, with Special Reference to Rheumatic Myocarditis. Lancet, 237: 305, 1939.

26. Levy, R. L. and Barach, A. L.: The Therapeutic Use of Oxygen in Coronary Thrombosis. J.A.M.A., 94: 1363, 1930.

27. Campbell, J. M. H. and Poulton, E. P.: The Effect on Breathless Subjects of Residence in an Oxygen Chamber. Quart. J. Med., 20: 141, 1926–1927.

28. Richards, D. W. and Barach, A. L.: Prolonged Residence in High Oxygen Atmospheres. Quart. J. Med., Vol. III, No. 11; July, 1934.

29. Barach, A. L.: Physiological Methods in the Diagnosis and Treatment of Asthma and Emphysema. Ann. Int. Med., Vol. 12, No. 4, 1938.

30. Meakins, J. and Christie, R. V.: Treatment of Emphysema. J.A.M.A., 103: 384, 1934.

31. Evans, J. H : Disease, The Inhalation of Pure Oxygen in the Treatment of Pneumonia. Canadian M. A. J., April, 1930; The Therapeutic Value of High Concentration of Oxygen in Pneumonia, Cardiac Decompensation, Asthma, Hay Fever and Other Diseases. Am. Med., 24: 211, 1929.

32. Sayers, R. R.: Personal communication.

33. Fine, J., Hermanson, L. and Frehling, S.: Further Clinical Experiences with Ninety-five per cent Oxygen for the Absorption of Air from the Body Tissues. Ann. Surg., 107: 1, 1938.

34. Boothby, W. M., Mayo, C. W. and Lovelace II, W. R.: One Hundred Per Cent Oxygen. J.A.M.A., 113: 477, 1939.

35. Alvarez, W. C.: Use of Oxygen in the Treatment of Migraine. Proc. Mayo Clinic, 14: 173, 1939.

36. Barach, A. L., Martin, J. and Eckman, M.: Positive Pressure Respiration and Its Application in the Treatment of Acute Pulmonary Edema. Ann. Int. Med., 12: 754, 1938.

37. Woodman, M.: On the Control of Air Pressure in the Lungs after Tracheotomy. J. Laryng. and Otol., 50: 214, 1935.

38. Kernan, J. D. and Barach, A. L.: Rôle of Helium in Cases of Obstructive Lesions in the Trachea and Larynx. Arch. Otol., 26: 419, 1937.

39. Barach, A. L. and Swenson, P.: Effect of Breathing Gases Under Positive Pressure on Lumens of Small and Medium-Sized Bronchi. Arch. Int. Med., **63**: 946, 1939.

40. Barach, A. L.: Use of Helium in the Treatment of Asthma and Obstructive Lesions in the Larynx and Trachea. Ann. Int. Med., **9**: 739, 1935.

41. Barach, A. L.: The Therapeutic Use of Helium. J.A.M.A., **107**: 1273, 1936.

42. Maytum, C. K., Prickman, L. E. and Boothby, W. M.: Use of Helium and Oxygen in the Treatment of Severe Intractable Asthma. Proc. Staff Meet., Mayo Clinic, **10**: 785, 1935.

43. Schwartz, A. L.: The Relief of Status Asthmaticus by Helium. J. of Med., Cincinnati, Ohio, May, 1938.

44. Eversole, U. H.: The Use of Helium in Anesthesia. J.A.M.A., **110**: 878, 1938.

45. Bonham, R. F.: The Value of Helium as an Adjunct in General Anesthesia. Anes. and Anal., January–February, 1939.

46. Metz, C. W., Wearner, A. A. and Evans, A. E.: Therapeutic Use of Helium. S. Med. J., **32**: 34, 1939.

47. Boch, J.: Symptomatic Treatment of Bronchial Asthma in Asthmatic Bronchitis. M. Bull. Vet. Admin., **14**: 48, 1937.

48. Barach, A. L.: Recent Advances in Inhalation Therapy in the Treatment of Cardiac and Respiratory Disease; Principles and Methods. N. Y. State J. of Med., **37**: No. 12, 1937.

49. Eckman, M. and Barach, A. L.: Technique of Inhalational Therapy. Modern Hospital, **52**: No. 2, 1939.

50. Himwich, H. E., Alexander, F. A. D. and Lipetz, B.: Effects of Acute Anoxia Produced by Breathing Nitrogen on the Course of Schizophrenia. Proc. Soc. Exp. Biol. and Med., **39**: 367, 1938.

51. Hinsie, L. E., Barach, A. L., Harris, M. M., Brand, E. and McFarland, R. A.: The Treatment of Dementia Praecox by Continuous Oxygen Administration in Chambers and Oxygen and Carbon Dioxide Inhalations. Psychiatric Quarterly, **8**: 34, 1934.

CLINIC OF DRS. ALVIN F. COBURN AND LUCILLE V. MOORE

DEPARTMENT OF MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE PRESBYTERIAN HOSPITAL

THE PROPHYLACTIC USE OF SULFANILAMIDE IN RHEUMATIC SUBJECTS*

THE tendency for the rheumatic process to recur is a characteristic recognized by all students of the disease. These recrudescences follow and appear to result from hemolytic streptococcal infection of the upper respiratory tract.[1, 2, 3] It therefore seemed reasonable that the prevention of hemolytic streptococcal infections might prevent these rheumatic recrudescences. This supposition proved to be true for the authors' rheumatic subjects who moved to semi-tropical climates; however, when these people returned to New York City (during the spring months) and became reinfected with hemolytic streptococci, they again developed recrudescences.

The important problem in the care of the rheumatic subject, however, has remained unsolved; namely, the prevention of recrudescences among children of the lower economic levels who live in overcrowded sections of large cities in the temperate zone. The work of Domagk[4] and the availability of sulfanilamide made it possible in 1936 to attack this problem by the prophylactic administration of this drug. The purpose of this report is therefore to present the results of a three year study in the chemoprophylaxis of hemolytic streptococcal infections and rheumatic fever.

Levaditi and Vaisman,[5] Buttle, Gray and Stephenson,[6] and others, have demonstrated the effectiveness of sulfanilamide prophylaxis in Group A hemolytic streptococcal infection of

the mouse's peritoneum. Hoare[7] has pointed out that good protection is obtained if the mice are treated before and for three days after infection. Our studies[6] have indicated that guinea-pigs can be protected from Group C respiratory tract infections with sulfanilamide administered before and for two weeks after infection.' Our recent studies, using a more soluble derivative which was rapidly excreted, have shown that protection in the guinea-pig is dependent upon maintenance of an adequate blood level. Thomas and France[9] have reported encouraging results on the prophylactic use of sulfanilamide in patients susceptible to rheumatic fever.

PROCEDURE

Selection of Patients.—Two prerequisites were sought in the groups of children selected for this study: (1) that each individual had experienced frank attacks of rheumatic fever with carditis, and (2) that each could be under close observation during the period of study. Preference was given to children who had experienced frequent or even annual attacks since the onset of the disease. The 1936 group consisted of twenty-nine rheumatic girls between the ages of six and fourteen who were convalescing in the Pelham Home. Two groups were studied in 1937: one group consisted of twenty-six children at the Pelham Home, and the other consisted of thirty who were attending classes for children with heart disease in a New York School.

The observations made during these two years[6] were sufficiently encouraging to warrant a more extensive study. Subsequently we have treated 104 additional rheumatic subjects of susceptible age, most of whom had already experienced more than one rheumatic attack. These included twenty-nine girls at the Pelham Home, twenty-two members of a class for cardiac children, and fifty-three school children scattered throughout the overcrowded tenements of Manhattan and the Bronx. Inasmuch as the most susceptible subjects were selected for treatment, they might be expected to have more infections and attacks than the control group. It was felt that this inequality in selection would merely add weight to any prophylactic effects that might be observed.

Observations.—1. *Clinical observations* were made each school day by a nurse or teacher, and every patient was examined at least twice monthly by the authors.

2. *Throat cultures* were taken just before beginning medication and at frequent intervals thereafter. At the Pelham Home, two cultures were taken each week, and in the New York City groups two or more per month. In addition, cultures were obtained at the onset of each respiratory infection.

3. *Erythrocyte sedimentation rates* were determined twice a month.

4. The *blood level of free sulfanilamide* was measured twice a month.

5. *Antistreptolysin titers* were determined at least twice a month. Following respiratory infections these tests were made twice a week.

Administration of Drug.—Sulfanilamide (Winthrop) was used throughout this study. Three doses were given daily, approximately at 7 a.m., 2 p.m. and at 8 p.m. throughout the school year (October to July). Most of the children received 3 gm. each day; some of the smaller children took only 2 gm. The blood levels were maintained at approximately 4 to 5 mg. per cent.

Toxic symptoms appeared in about 10 per cent of each group within a few days after starting medication. These symptoms were of two types: Some children developed classical manifestations of sulfanilamide sickness; others convalescing from recent attacks developed rheumatic recrudescences. The patients who tolerated the drug for two weeks remained symptom-free thereafter, and were kept under medication for the experimental period. Those few who developed drug symptoms were taken off the drug and transferred to the unmedicated control group. Except for the possible failure to gain weight in some instances, no untoward effects were noted from prolonged administration of sulfanilamide.

RESULTS

Attempts were made to determine whether the drug influenced either the incidence of streptococcal infection or the incidence of rheumatic attacks, or both, and comparisons were made from several points of view:

1. **Family Outbreaks of Hemolytic Streptococcal Infection.**—It was not possible to determine how many of the families of our treated patients were infected with hemolytic streptococci; it was possible, however, to collect bacteriologic evidence indicating that in at least ten families there occurred hemolytic streptococcal outbreaks in which the members receiving sulfanilamide escaped infection.

2. **Incidence of Upper Respiratory Infection with Hemolytic Streptococci.**—The variability of infection with hemolytic streptococci from year to year and in different economic groups is well recognized. Our studies from 1928 to 1938 have shown wide fluctuations with an average between 30 and 40 per cent infected. In the period 1936–1938 the incidence of infection in an untreated group of 400 individuals was approximately 35 per cent and, in 1939, it was 35 per cent in a smaller group.

Three per cent of our patients treated with sulfanilamide contracted infections which could be ascribed to hemolytic streptococci on account of either bacteriologic or serologic evidence. In most of these children two or more pathogens were present. Carriers of hemolytic streptococcus remained carriers over a period of months after treatment began. Approximately 6 per cent of the group had a few hemolytic organisms in the throat flora on one or more occasions without, however, any evidence of infection.

3. **Incidence of Rheumatic Attacks.**—The control group in 1939 comprised 129 rheumatic subjects, mostly adolescents and young adults. During the period of study half of these patients showed signs of hemolytic streptococcal infection and half escaped. There were 15 per cent in whose throat flora hemolytic streptococci appeared in large numbers without causing symptoms and 35 per cent in whom there was both clinical and bacteriologic evidence of hemolytic streptococcal infection. About half of the patients with clinical infections developed rheumatic fever, resulting in a 20 per cent incidence of rheumatic attacks for this group of 129 subjects.

These patients were of an age commonly less susceptible to rheumatic attacks. The data furnished by a group of children is therefore of particular interest. Seventeen children who were treated during 1937 and not treated during 1938 and

1939 gave an indication of the expected incidence of rheumatic attacks in the lower age group. The incidence of hemolytic streptococcal infection was 47 per cent and of rheumatic attacks 35 per cent. These observations are shown in Table I.

TABLE I

THE INCIDENCE OF HEMOLYTIC STREPTOCOCCAL INFECTIONS AND RHEUMATIC ATTACKS IN 17 PATIENTS DURING MEDICATION AND AFTER DISCONTINUING MEDICATION

	1937 Treated.	1938 Untreated.	1939 Untreated.
Hemolytic streptococcal infection...................	0	7	8
Rheumatic attacks..........	0	5	6

The *erythrocyte sedimentation rates* of treated patients remained normal in almost the entire group. A few rises accompanied respiratory infection; one accompanied a rheumatic attack and one was unexplained. The *antistreptolysin levels* remained almost constant throughout the experimental period. The patient with the rheumatic attack developed an antistreptolysin titer which rose slowly from 200 to 625 units over a period of two months. Two patients with mixed infections showed a rapid but moderate rise in titer.

The *incidence of rheumatic attacks* among medicated patients was low. Only one of 184 subjects developed rheumatic fever. The expected incidence of attacks in rheumatic children of this age in New York City has in our experience been approximately 35 per cent.

SUMMARY

Sulfanilamide was given to children throughout the school year and a blood level of about 4 mg. per cent was maintained without detectable harmful effect.

These blood levels were accompanied by almost complete protection against hemolytic streptococcal infection in 184 children studied between 1936 and 1939.

The incidence of rheumatic fever in this group with an expectancy of 35 per cent was less than 1 per cent.

BIBLIOGRAPHY

1. Glover, J. A.: Lancet, 1: 499, 1930.
2. Collis, W. R. F.: Lancet, 1: 1341, 1931.
3. Bradley, W. H.: Quart. J. M., new series, No. 1, 79, 1932.

4. Domagk, G.: Deut. med. Wchnsch., **61**: 250, 1935.

5. Levaditi, C. and Vaisman, A.: Compt. rend. Soc. Biol., **121**: 803, 1936.

6. Buttle, G. A. H., Gray, W. H. and Stephenson, D.: Lancet, **1**: 1286, 1936.

7. Hoare, E. D.: Lancet, **1**: 76, 1939.

8. Coburn, A. F. and Moore, L. V.: J. Clin. Invest., **18**: 147, 1939.

9. Thomas, C. B. and France, F.: Bull. of Johns Hopkins Hospital, **64**: 67, 1939.

CLINIC OF DR. YALE KNEELAND, JR.

Presbyterian Hospital

THE TREATMENT OF PNEUMONIA WITH SULFAPYRIDINE

In May, 1938, L. E. H. Whitby, an English worker, announced that a sulfonamide derivative, 2(p-amino benzene-sulfonamido) pyridine, called by him "M & B 693," was an effective therapeutic agent against pneumococcic infection in mice, and very shortly thereafter its successful use in human pneumonia was reported. Within a few weeks supplies of the drug were available for clinical trial in America, and in the little more than a year that has elapsed since its introduction, a remarkably large literature has accumulated relating to its activity in pneumococcic and other infections, both experimental and clinical. Broadly speaking, all these publications have tended to confirm the original observations of Whitby, and it is safe to say that the drug, officially designated as "sulfapyridine" in this country, has become generally accepted as a highly important weapon in combating infections caused by all types of pneumococci as well as certain other organisms. It is the purpose of this paper to describe its use in treating pneumococcic pneumonia in man.

It is unnecessary here to undertake any detailed discussion of the mode of action of the drug. This is a subject which is still a matter of intensive study, and it is sufficient to point out that, like sulfanilamide in relation to hemolytic streptococci, sulfapyridine is not actually bactericidal for the pneumococcus. It has a very definite bacteriostatic effect, however, and it is generally believed that it creates in the body of an infected animal conditions adverse to the full activity and multiplication of pneumococci, thereby permitting the ordinary

defensive mechanisms of the host successfully to deal with the invader. Sulfapyridine appears to possess this activity against all types of pneumococci. Although there is evidence that some types, as well as certain different strains of the same type, are less affected than others, this does not appear to invalidate the general principle that sulfapyridine is useful in all infections due to the pneumococcus.

The results of treatment of pneumococcic pneumonia with sulfapyridine have now been published in a number of large series of cases, and these may be roughly summarized by the statement that the mortality rate runs around 5 per cent. In view of the fact that the previously reported mortality rate in lobar pneumonia among adults to whom no specific treatment was given was never less than 20 per cent, it is evident that the drug is beyond all question an agent of the utmost value. From a study of the cases reported in which death took place in spite of treatment, it is apparent that these failures have often occurred where treatment was begun late or dosage was inadequate. This raises the question as to whether under ideal circumstances of early treatment and adequate dosage, sulfa-pyridine alone might save every patient. It is the author's belief that it would not, that fulminating cases in highly susceptible individuals, in the aged, or in the alcoholic, will still end fatally from time to time. Nevertheless, it is my belief that under ideal circumstances the mortality rate in lobar pneumonia may be reduced by means of sulfapyridine treatment to the neighborhood of 2 or 3 per cent.

Indications and Contraindications.—The criteria by which cases are selected for treatment are extremely simple. Let us begin with the *contraindications:* In our experience the only contraindication is a history of *previous sensitivity** to sulfanilamide or its derivatives. In other words, we do not believe that anemia, leukopenia, jaundice, etc., are contraindications *provided they are already in existence before the drug is started* (and are therefore not manifestations of drug sensitivity). Patients with all these pre-existing conditions have been treated in this clinic when the situation warranted without untoward result.

* As manifested by a history of severe febrile reaction, hemolytic anemia. neutropenia, or jaundice.

The *indications* for treatment are as follows: 1. *Lobar pneumonia.*—All patients giving the typical history and clinical picture of lobar pneumonia are started on sulfapyridine therapy as soon as sputum is obtained for typing and blood for culture. If a rapid sputum typing can be obtained at once, it is good practice, theoretically at least, to delay therapy until one is sure one is dealing with pneumococcus lobar pneumonia. However, if the clinical picture is clear-cut, it seems to us that one is justified in commencing therapy, particularly in a patient who is quite ill, in the absence of a definite sputum typing. The physician, however, should continue to make every effort to determine the type of infecting organism. 2. *Bronchopneumonia.*—In the early stages of bronchopneumonia it is advisable to withhold treatment until adequate bacteriologic studies have been made. This rule, however, may be abrogated where the situation is desperate or sputum is unavailable, such as may occur, for instance, in postoperative cases, the very young, or the very old.

Results to Be Expected.—What may one expect, then, in a case of lobar pneumonia adequately treated with sulfapyridine? The answer to this question is simple: *within twenty-four hours,* in about half the cases, the temperature will have fallen to normal, the pulse and respiration will be lower, and clinical improvement will be manifest. In the remaining cases, while some evidence of improvement will be discernible within twenty-four hours, the temperature will not reach normal until forty-eight or seventy-two hours have elapsed—the fall in temperature having more the appearance of "lysis" than "crisis."

Failure of this expected result to occur indicates, in our experience, one of four conditions: 1. One is not dealing with pneumococcus lobar pneumonia. 2. A complication is present. 3. Dosage is inadequate (as measured by blood level, not by amount of drug ingested). 4. The disease is of a fulminating type, and other measures are indicated in addition to sulfapyridine. By all odds the most common of these is No. 1.

To repeat, then, the administration of sulfapyridine will produce, in nearly every case of lobar pneumonia, a temperature chart which has the appearance of cure by crisis or rapid lysis. It must be emphasized, however, that *the patient docs*

not look as well as his temperature chart. While he is very obviously better than before treatment, he is not as remarkably improved as would be the case if the crisis were a spontaneous one. This is partly due to the depression caused by the drug, but one also has the impression that the disease, while greatly modified, is still going on, and in support of this belief is the fact that signs of consolidation persist longer than they do in the case of a spontaneous crisis. It is also well recognized that if treatment is stopped at this stage, a sharp recrudescence may take place.

As far as the precise method of treatment is concerned, it must be emphasized that there is no hard and fast rule that will fit every case. The effectiveness of the drug depends on the establishment and maintenance of an *effective level* of the free compound in the *blood stream.* Individual patients may vary widely in their rate of absorption and excretion of sulfapyridine. Moreover, the drug is detoxified in the body by acetylation, and patients also vary widely in the proportion of free to acetylated drug recovered in the blood serum. As it is only the free drug that appears to be active, this factor of *rate of acetylation* must also be considered in relation to dosage. In spite of these rather formidable-sounding difficulties, however, a reasonably satisfactory routine has been worked out which seems to work well in the average patient.

Method of Administration.—It has been our practice in dealing with *adults* to start with an *initial dose* of 2 gm. (gr. xxx) p.o. and then continue with 1 gm. (gr. xv.) every four hours day and night. Where the situation seems of great urgency, the initial dose may be increased to 4 gm. (gr. lx).

In *hospital practice,* where there is an available laboratory for blood-serum sulfapyridine determination, an estimation of the amount of free drug in the patient's serum is made the morning after treatment has been started and the dosage is regulated according to the result. One or two subsequent determinations are also made during the course of the disease. Our object in therapy is to maintain a level of free drug in the blood stream of around 5 mg. per cent. A study of case records in this clinic would seem to indicate that lower levels than this, such as 3 mg. per cent, are therapeutically effective in lobar pneumonia of average severity; nevertheless, it is

advisable to aim at 5 mg. per cent if possible. If the blood level of the free drug on the usual dosage should go higher than 7 mg. per cent, it is well to reduce the dosage except in very severe cases, in view of the fact that there appears to be some relationship between toxic manifestations and high blood concentrations. (When dealing, however, with *really desperate* types of infection, such as pneumococcic meningitis, it is our belief that considerably higher concentrations are obligatory.)

It is quite obvious to the writer that thousands of cases of pneumonia must of necessity be treated with sulfapyridine under circumstances *where blood determinations of the drug cannot be made*. For such situations the following rules of thumb might be drawn up:

1. Give the standard dosage of 6 gm. daily in every case, and maintain this dosage for about four days. Then halve the dose, giving 3 gm. daily in six doses, for three or four days more.

2. If a very obvious effect is not noticeable in twenty-four hours; (*a*) question the diagnosis, (*b*) look for a complication, and then (*c*) if nothing new turns up, assume the blood level is too low and increase the dose by 2 or 3 gm. for a day or so, *provided no contraindications are present* (*i.e.* no severe toxic manifestations). It must be re-emphasized, however, that the most intelligent handling of these cases is achieved with the aid of blood level determinations.

A few other notes on dosage might be in order here: *children* tolerate the drug, on the whole, much better than adults, and it is customary to give somewhat larger doses per pound of body weight (infants, perhaps, twice the amount of drug per pound as the average adult, and small children one and a half times). *Very old* individuals often build up extremely high blood levels on the usual dosage, presumably through faulty elimination, and in this age group the dosage of the drug must be regulated with *special caution*. It is also worthy of remark that Type III pneumococcic pneumonia in the aged responds to sulfapyridine, but it does so sluggishly, and it is frequently necessary to administer the drug guardedly to such individuals over a very long period of time in order to achieve resolution.

Other Measures of Therapy.—It goes without saying that the other measures in the treatment of lobar pneumonia are carried on as usual: the *administration of fluids, control of cough* and *distention, oxygen* where indicated, and *supportive therapy* in general.

In addition, however, there are certain problems introduced by the drug itself which may need special management: As is well known, *nausea* and *vomiting* occur in a considerable number of cases, and occasionally the latter is very persistent indeed. Under such circumstances, special sedation is necessary, and we have found that hyoscine, 0.0004 gm. (gr. 1/150) given hypodermically, followed by an occasional dose of sodium luminal, 0.06 gm. (gr. i) also by hypo, often controls the symptoms very satisfactorily.

The use of moderate doses of *bicarbonate of soda* administered simultaneously with sulfapyridine was orginally recommended to overcome the supposed acidosis produced by the drug. This has been abandoned as a routine measure in this clinic; however, in many cases it is still employed to allay gastric irritability. Theoretically, also, it seems wise to alkalinize the urine in order to lessen the possibility of massive precipitation of the drug in the renal pelves. Lastly, it must be borne in mind that, owing to gastric intolerance, dehydration and disturbances in the acid-base equilibrium may ensue, and must be corrected by the administration of *parenteral fluids*.

Intravenous Administration of Sulfapyridine.—All of the foregoing discussion has related to the oral administration of sulfapyridine, and it is well to remark now that there has been recently introduced a sodium salt of the drug which is very soluble and which is therefore suitable for intravenous use. In our experience the vast majority of cases of pneumonia can be handled by the oral method of treatment alone; however, there are situations wherein *sodium sulfapyridine*, administered by vein, is of great value. These may be summarized as follows: 1. Where one is dealing with an *extremely sick* patient in whom one wishes to achieve a maximal effect as rapidly as possible. 2. Where, for one reason or another, the drug *cannot be taken by mouth.* 3. In *pneumococcic meningitis*, where a very high blood level is desired at once. Under

these circumstances sodium sulfapyridine in 5 per cent solution may be given intravenously* in a dose of 5 gm. Following such a dose, it is usually possible to maintain the desired blood level by oral administration; if not, the intravenous method may be repeated as often as necessary.

Duration of Treatment.—The tendency for lobar pneumonia to recrudesce if treatment is discontinued too soon has already been mentioned and reference has also been made to the proper duration of therapy. It is worth referring to these points again, for the temptation to stop treatment in an individual who experiences considerable discomfort from the drug is very great indeed. Here again one cannot make hard and fast rules. It is our belief that the average patient does best on about *four days* of *full dosage*, followed by *half dosage* for *three* or *four days more*. This dosage may safely be lessened in certain cases of very mild pneumonia; or it may be necessary to extend the course of treatment if complications are present or, as was said above, in Type III pneumonia of the aged. The physician, as his experience with the drug increases, will find it increasingly easy to make these decisions himself.

One more word may be said in regard to *complications:* It is our belief that the incidence of suppurative complications of lobar pneumonia will be greatly lessened by early treatment with sulfapyridine. However, it has been our experience that if *empyema*, for instance, develops, the usual surgical drainage will ultimately be necessary, although sulfapyridine unquestionably modifies and ameliorates the course of this complication. Small sterile pleural effusions have incidentally been noted from time to time in treated cases; these resorb in due course without incident.

Type-Specific Serum Therapy.—Finally, the advisability of type-specific serum therapy in addition to sulfapyridine must be briefly discussed. This is a controversial subject about which it is impossible to be dogmatic. There is evidence that the beneficial effects of the drug are enhanced if it operates in the presence of specific antibodies. On the other hand, it has been our experience that the *great majority* of patients

---

*This solution is quite alkaline, and great care must be taken *not to infiltrate the tissues around the vein* or sloughing will ensue.

with lobar pneumonia will recover promptly on drug treatment alone, thereby making the costs, the complications, and the hazards of serum therapy unnecessary.

Nevertheless, there will certainly continue to exist *cases in which serum is indicated,* cases which might roughly be classified as follows: 1. Cases in which sulfapyridine is contraindicated by virtue of sensitivity to the drug (*q.v.*). 2. Maximally severe cases. It is a little hard to define this group precisely, apart from the statement that if the onset is fulminating, if the patient is unusually prostrated and toxic, if the early involvement of lung is very extensive, or if a heavy bacteremia is known to be present, the case may be regarded in this category. With *bacteremic* cases, it is our own custom to treat with serum if a very definitely beneficial effect of sulfapyridine is not evident within twenty-four hours. Again, this is a situation wherein the physician must depend on his own experience and judgment.

Toxic Manifestations.—Such are the principles of the treatment of lobar pneumonia which have been worked out and generally agreed to in this clinic during the past year. Before closing the presentation, however, it is necessary to indicate the untoward side-effects of sulfapyridine, together with their significance. These toxic manifestations are generally similar to those caused by sulfanilamide which have been so often described in the literature. It is our feeling, incidentally, that sulfapyridine *is no more dangerous* than sulfanilamide, in spite of the fact that patients taking the new drug feel, on the average, a good deal sicker than those on the old. For the sake of convenience, these toxic manifestations will be listed in tabular form:

GENERAL EFFECTS.—*Cyanosis.*—Due to an altered condition of the blood pigment, cyanosis occurs, but is less conspicuous than with sulfanilamide. It may be disregarded.

Depression.—Almost all patients on sulfapyridine report a variable degree of physical and mental depression. Occasionally this is very marked.

Nausea and Vomiting.—Many patients complain of nausea. A considerable number actually vomit. Occasionally these symptoms are very severe and distressing. Methods for their control have already been suggested, and it is rarely necessary

to discontinue the oral administration of sulfapyridine on their account. The vomiting, incidentally, appears to be chiefly central in origin, and may occur when the drug is given intravenously.

SPECIAL EFFECTS.—*Hematuria.*—This has been reported in a few cases, and may be accompanied by renal colic. It appears to be due to massive crystallization of acetylsulfapyridine in the urine, with the formation of numerous small calculi in the renal pelves and ureters. Suppression of urine with uremia and death have been reported in one case. While a very few red cells in the urine may be disregarded, their appearance in any *considerable numbers* is an indication for immediate discontinuance of the drug. It has not yet been shown that the use of alkalis, which is theoretically indicated, will lessen the frequency of this complication. The most important thing to bear in mind is that *daily urine examinations are indicated during treatment.*

MANIFESTATIONS OF SENSITIVITY.—*Fever.*—Fever due to sulfapyridine resembles that due to sulfanilamide, and is noted with about the same frequency. It occurs as a rule after seven to ten days of therapy, but may appear quite a little earlier or much later. It often presents an extremely difficult problem in differential diagnosis, for it may be accompanied by a leukocytosis and, in that case, mimics the disease that is being treated. Generally speaking the patient does not look quite as ill, and his pulse rate may not be as high, as if the fever were due to a flaring up of uncontrolled infection. It is a safe rule to regard any *unexpected and unexplained event occurring during the course of sulfapyridine therapy as due to the drug unless proved otherwise.* The treatment of sulfapyridine fever is to discontinue the drug, and the temperature may be expected to fall within twenty-four hours. The prognosis is good.

Rash.—This is usually morbilliform in character, and occurs as a rule in conjunction with sulfapyridine fever. If present, it simplifies the diagnosis.

Hemolytic Anemia.—Very severe acute hemolytic anemias have been reported, often occurring after only a few days of treatment. While a drop of a few hundred thousand in the red cell count may be disregarded, a sudden drop of a million

or more, particularly if accompanied by acholuric jaundice. *is an absolute indication for discontinuance of treatment.* If this is done at once the prognosis is good, although transfusion may be necessary. *Daily blood counts should be done in all cases while under treatment.*

Neutropenia.—A moderate drop in the total white cell count may be disregarded. However, severe agranulocytosis, which may actually be fatal, has been described. Here again, the essential precaution is the *daily blood count.* Agranulocytosis usually develops later than hemolytic anemia, and may occur after several weeks of therapy or even after therapy has been stopped. Naturally, further drug treatment is absolutely contraindicated in the presence of this complication.

Hepatitis.—We have observed an occasional patient developing jaundice with dark urine and fever after several days of intensive sulfapyridine therapy. Presumably this jaundice is due to hepatitis. It is an indication for immediate cessation of treatment. The prognosis, apparently, is good.

A review of these toxic manifestations indicates that sulfapyridine, like sulfanilamide, is a potentially dangerous drug, which should be used only under the *strictest supervision* of an experienced physician. The serious complications, fortunately, are rare but they must be watched for with unrelenting vigor

CLINIC OF DR. HENRY E. MARKS

METABOLISM SERVICES OF THE CITY HOSPITAL AND THE
PRESBYTERIAN HOSPITAL

A NEW GLOBIN INSULIN. THE IMPORTANCE OF CARBOHYDRATE DISTRIBUTION IN THE CONTROL OF DIABETES WITH THE MODIFIED INSULINS

THE modified insulins have proved themselves valuable new tools for the treatment of the diabetic patient. But the full possibilities of a new tool become apparent only when the new technics necessary for its most effective use have been worked out by observation and experience. This is especially true of the retarded insulins; they are technically more difficult to use than regular insulin because carbohydrate and insulin action must be kept in balance over a much longer period. Various devices have been resorted to for overcoming this difficulty, but the experts still differ as to the most satisfactory method. Some of them remain pessimistic as to the possibility of complete regulation with these preparations alone, and failure to find an effective technic keeps many physicians and patients from reaping the benefits of their use.

The chief advantage of a retarded insulin is its ability to control the blood sugar level throughout a twenty-four-hour period with a single dose. If it cannot do this, it has no real advantage over ordinary insulin. Theoretically it should be possible to accomplish this by distributing the daily carbohydrate in such a way as to balance insulin activity at each period of the day. Since this method has worked out well and has permitted the regulation of most of our diabetics on one daily dose, it seems worth while to describe the technic. I also wish to describe a new retarded insulin with certain advantages over those now available.

649

Working Principles in the Treatment of Diabetes.— I should like to begin by setting down a number of working principles we have come to accept:

1. The *object of treatment* is maintenance of a normal blood sugar level throughout the twenty-four hours; for this purpose the normal range of blood sugar may be taken as 70 to 150 mg. It is not enough to keep the urine sugar-free if the blood sugar remains much above this level.

Regulation has been checked by determining the blood sugar level four times in the twenty-four hours, before each meal and at bedtime. Postprandial blood sugars are also studied, at times, to determine the height of hyperglycemia after meals; a brief rise above the 150 mg. level at this time is without significance, even though a trace of glycosuria may occur. In some patients this cannot always be avoided when a slow-acting insulin is used, without increasing the dose to a point which produces hypoglycemia before meals. Such traces of glycosuria may be neglected if the a.c. blood sugars are normal.

2. In order to *assess the value of an insulin preparation,* one must work with patients who are well stabilized, who have no infections or complications of such a nature as to affect carbohydrate tolerance, and whose insulin requirement has reached a fixed level.

3. The *diets* in such experiments should furnish a maintenance level of calories and of protein. The distribution of protein and fat between the various meals is not important, but *carbohydrate distribution* is of great importance and must be accurate. Our routine diets supply from 60 to 100 gm. of protein; from 150 to 200 gm. of carbohydrate (unless special indications call for a lower or a higher level), and sufficient fat to make up the caloric requirement.

4. Patients differ in their *rate of reaction* to insulin. *The optimal distribution of carbohydrate consequently must be worked out individually for each patient.*

5. Certain patients, particularly children and adolescents, tend to be *inherently unstable.* Instability is of two kinds, often coexistent. One is due to *insulin hypersensitiveness,* with exaggerated swings of the blood sugar level after carbohydrate and after insulin; the other is characterized by irreg-

ular *variations from day to day in carbohydrate tolerance and insulin requirement.* The first type may be dealt with more or less successfully by interval feedings to control hypoglycemia. The second type, unless due to intercurrent infection or other complications, is difficult to treat and may make successful control impossible. With the second type of instability one must always suspect surreptitious variations in food intake, errors in the serving of the diets, or variations in the technic of injection of the depot insulins. It is important that these injections be made into the *subcutaneous space,* and not into the deeper layers of the skin, and we prefer to have the site lightly massaged after the injection. Some patients, especially the younger ones, may be highly sensitive to variations in the amount of physical exercise, and Joslin[1] has called attention to the possibility of delayed hypoglycemia on the day following unusual exercise when retarded insulin is used. But apart from these considerations, there are undoubtedly patients who have a genuine variability of insulin requirement from day to day.

Instability often diminishes spontaneously, especially in adolescents as they reach maturity, and many unstable patients become progressively more stable as careful management improves control. These patients are often less likely to have severe shocks when treated with the slower-acting types of insulin, and at times the change to a retarded insulin has itself a remarkably stabilizing effect. In other cases reduction of carbohydrate from a high level to a moderate or low level results in a marked gain in stability. All these measures should be tried in handling such patients.

Regular Insulin.—The properties and characteristics of ordinary insulin are familiar to you all. The points that concern us here are these:

1. Its *action begins quickly* in most patients, particularly after the overnight fast; it must therefore be followed by food *within fifteen or twenty minutes.* Insulin-sensitive patients may become hypoglycemic within ten minutes after the injection. but insensitive patients react slowly and will develop hyperglycemia and glycosuria after breakfast unless the injection is taken earlier, often as much as an hour before the meal. *Maximum action,* and consequent lowering of blood sugar, usu-

ally occurs from three to five hours after the dose. In some patients the action is so delayed and prolonged that the morning dose shows very little effect until afternoon and is still active in the evening. To regulate these patients glycosuria after breakfast must be controlled by increasing the evening dose of insulin; glycosuria in the evening is controlled by increasing the morning dose.

2. Most patients are best controlled by *equal division* of *carbohydrate* between the three meals, with insulin before the morning and evening meals, the morning dose usually being the larger. Variation in the rate of action in different patients may require modification of carbohydrate or insulin distribution. A high degree of insulin sensitivity, with consequent hypoglycemia about three hours after breakfast, is best dealt with by dividing the breakfast carbohydrate, giving a portion of fruit as a midmorning feeding. The evening meal may require similar division.

3. A *third dose of insulin* is not ordinarily required. When it is necessary it should be given at 11 or 12 o'clock at night with a small carbohydrate feeding. This is necessary only for patients who are so sensitive to insulin that a dose large enough to control the blood sugar throughout the night cannot be given without provoking hypoglycemia during the evening. The very unstable diabetic may require five or six feedings in the twenty-four hours to maintain a fairly constant blood sugar level.

4. Regular insulin is preferable to the *slow-acting insulins* in patients whose *food intake may vary from day to day*, since the dosage can be more easily adapted to the immediate requirement. This applies especially to the surgical diabetic, in pregnancy, in acute infections, and when complicating illness, nausea, or vomiting are likely to affect food intake.

Protamine Zinc Insulin.—The combination of insulin with protamine and zinc produces a suspension which is only slowly soluble at the *p*H of the body tissues. This not only results in a prolonged steady insulin effect. but also increases the total value of the dose, just as dividing a single dose of regular insulin into a number of smaller doses increases its effectiveness. The insulin requirement is therefore likely to be somewhat less than when regular insulin is used.

Protamine insulin would be more widely used. and to

greater advantage, if the modifications in technic required for best results were better appreciated. The most common source of difficulty is the attempt to shift from regular insulin to protamine *without sufficient alteration in carbohydrate distribution*. If the patient has been on three approximately equal meals, the change to protamine then results in glycosuria in the early part of the day and hypoglycemia at night. Various devices are used for dealing with this situation, the most common being the use of a supplementary dose of regular insulin with the protamine in the morning, and often additional doses of protamine or regular insulin, or both, at suppertime. But with these methods of solving the problem management becomes more troublesome for the patient and less effective than when the ordinary two-dose scheme with regular insulin is used. The physician therefore is likely to abandon the attempt to use protamine.

I wish to show that it is not difficult to achieve satisfactory control of the blood sugar on one dose of protamine zinc insulin if the basic principle is kept in mind that *the distribution of carbohydrate must accord with the intensity of insulin action as it varies during the course of the day*.

When injected at breakfast time, the intensity of insulin action during the morning is relatively feeble; the breakfast carbohydrate must therefore be small. By midday, the effect has increased, and in some patients has reached its maximum, and it then remains fairly constant until late at night. Lunch and dinner must therefore supply the largest amounts of carbohydrate, and the long interval between dinner and breakfast must be broken by a bedtime feeding if hypoglycemia in the early morning hours is to be avoided.

A search of the literature reveals general failure to recognize the basic importance of working out the *optimal carbohydrate distribution for each patient individually*, and failure to realize that most patients can be controlled on one daily dose when this is done. Lawrence,[2] for example, finds it necessary to use multiple doses in most cases. Only in the mildest ones, requiring small doses, does he use protamine alone. In moderately severe cases he combines regular insulin with the morning dose of protamine, and in more severe cases he may use a dose of regular insulin in the evening also. He finds

with this method that one must be satisfied with partial control of glycosuria and concludes that full control is impracticable because of the danger of nocturnal hypoglycemia. He says: "When the basal dose has been raised sufficiently to make the 8 a.m. urine sugar-free (and more we should not dare to give without risking hypoglycemia at night), the glycosuria by day persists heavily in all other samples of urine. . . . The action of the basal dose should be wearing off at night, and my experience has taught me that if the 8 a.m. urine is sugar-free two days out of three, the dose of zinc protamine insulin is large enough. If this specimen is always sugar-free and if the fasting blood sugar is usually completely normal, then sooner or later the patient will suffer from hypoglycemic attacks in the latter part of the night, often just before breakfast."

Joslin[1] likewise, in a series of sixty-two cases, found it possible to regulate only thirty-two on protamine alone, the other thirty requiring supplementary doses of regular insulin. He used interval feedings to prevent hypoglycemia but gives no data concerning carbohydrate distribution in his diets. White and Winterbottom[11] reported on 123 diabetic girls aged five to twenty years treated with protamine zinc insulin. Of this number only eleven were treated with protamine alone, 112 with protamine plus regular insulin. The diet was divided into three meals and three small lunches, no further data being given as to carbohydrate distribution. Pollack[3] and Pollack and Dolger[12] were able to control their patients with a single dose of protamine on a fixed carbohydrate distribution of ⅕—⅖—⅖ by eliminating from the diet fruit juices and similar forms of rapidly available carbohydrate and by giving one-half the total daily protein at the evening meal, with a bedtime meat feeding when necessary, and using fats to delay carbohydrate absorption. They found small shifts of carbohydrate from one meal to another necessary at times. Boyd and Jackson[4] and Gray[5] found it impossible to control the blood sugar level satisfactorily with one dose of protamine insulin in children. The latter found it necessary to use supplementary doses of regular insulin in most cases. Neuhoff and Rabinovitch[6] were able to control 50 per cent of a series of twelve patients on one dose of protamine insulin alone:

they considered the other 50 per cent unsuitable for protamine. They do not mention carbohydrate distribution in their diets, and, like most authors, do not seem to consider this a determining factor in controlling the blood sugar.

Some writers recognize the need for a small breakfast and a bedtime feeding, but almost all tend to use a standardized diet distribution. The ⅕—⅖—⅖ carbohydrate distribution, used by a number of writers,[3, 5, 7] sometimes with bedtime feedings when indicated, approaches the requirement of most patients, but I wish to emphasize that no fixed distribution can be universally satisfactory in using the retarded insulins.

The *optimal distribution of carbohydrate* must be determined for each patient by *observation of the urine and blood sugars.* Four daily urine specimens should be examined, one for each of the intervals between meals. Carbohydrate is shifted from one meal to another and insulin dosage adjusted until glycosuria is small in amount and uniform in all four specimens. Careful increase of the dose then renders the patient sugar-free. Blood sugars should now be determined, to guard against errors due to abnormally high or low renal sugar thresholds, and against the symptomless hypoglycemia which may occur in these patients. The blood sugar level before each meal is our guide to the amount of carbohydrate to be given at the previous meal.

Reduction of the blood sugar to a normal level is commonly followed by improvement in carbohydrate tolerance, and the second stage of regulation is normally characterized by hypoglycemia and progressive lowering of the dose until the patient reaches a stable level.

In this connection, it is my impression that the reduction of the blood sugar to hypoglycemic levels favors and hastens recovery of carbohydrate tolerance. Shocks are often unavoidable as the insulin requirement drops and adequate provision must be made for handling them. They are not to be feared; many of our patients have been elderly and arteriosclerotic, but I have never seen angina or thrombosis brought on by insulin shock, although one prefers to keep the blood sugar at a normal or high normal level when the myocardial circulation is impaired.

Characteristic of protamine insulin is the *carry-over* of a

considerable part of its effect to the second day, or even beyond. It is this carry-over that takes care of the following day's breakfast, before the new dose becomes effective. It must be reckoned that the *effective* acting dose on any day is made up of roughly *three-quarters of the dose given that morning plus one-quarter of the dose given the previous day.* This calculation becomes important when changing from regular insulin to protamine, or vice versa. In the first case it is wise to give 10 or 15 units of regular insulin at the same time as the protamine on the first day, and 5 or 10 units on the

PATTERN OF CARBOHYDRATE DISTRIBUTION REQUIRED TO OBTAIN A NORMAL AND FLAT BLOOD SUGAR CURVE WITH ONE DOSE OF PROTAMINE INSULIN

	PZI units.	CH daily.	CH distribution.	a. c.* blood sugars.
1.	47–0–0	201	24–45–66–66	125–118–118–133
2.	73–0–0	182	30–60–61–31	75–119–122–121
3.	10–0–0	150	40–40–40–30	78– 85–110–115
4.	37–0–0	152	31–50–50–21	91–129– 95–111
5.	78–0–0	152	21–36–50–45	84–120–148– 93
6.	40–0–0	150	30–40–50–30	118– 93–115–143
7.	30–0–0	152	25–40–45–40	87–125–154– 83
8.	18–0–0	150	40–45–30–26	105–114–132–119
9.	30–0–0	151	31–56–39–26	98–118–158–111
10.	15–0–0	150	25–45–45–35	129–123–124–118
11.	76–0–0	167	32–41–50–42	80–138–129– 80
12.	20–0–0	102	21–31–29–21	83–114– 85– 98
13.	0–0–26	150	38–50–42–21	78–111– 91–103
14.	40–0–0	152	26–40–55–31	114–111–105–111
15.	36–0–0	210	45–60–60–45	108–111–115–118
16.	50–0–0	150	25–40–40–50	108–121–114–122

* a. c.: before meals.

second day, to compensate for the absence of full carry-over effect; in the latter case one gives proportionately less than the anticipated dose of regular insulin for the first day or two.

I should like to illustrate here, by means of a typical group of patients, the pattern of carbohydrate distribution required to obtain a normal and flat blood sugar curve with one dose of protamine insulin. Each curve represents the final stabilization of a different patient.

It will be seen that the *breakfast carbohydrate* varies from 20 to 45 gm. The amount required is relatively constant for

in total carbohydrate. *Lunch* and *dinner* tend to be approximately equal. In seven of these cases they were equal, in six dinner was the larger meal, and in three lunch was the larger. This approximates quite well the general frequency distribution found in our experience. *Bedtime feedings* range from 21 to 66 gm., the majority between 25 and 40. Such feedings should be given in the form of slowly absorbed carbohydrate, such as bread or crackers and milk. Note that patient 13, who had his injection at suppertime, required the same type of carbohydrate distribution as the others. This has been our experience with other patients who have had the injection in the evening.

An occasional patient is found who can dispense with the bedtime feeding. These patients seem to dispose of their in-

CARBOHYDRATE DISTRIBUTION IN CASES NOT REQUIRING A
BEDTIME FEEDING

	PZI units.	CH daily.	CH distribution.	a. c. and bedtime blood sugars.
1.	24-0-0	149	49-50-50	80-138- 89- 84
2.	40-0-0	152	51-51-50	85-100- 83- 89
3.	60-0-0	200	35-65-100	105-103-121-121
4.	75-0-0	149	33-45-71	72-118-111- 89
5.	20-0-0	100	25-30-45	93- 86- 93-119
6.	20-0-0	102	20-40-40	103- 91- 85- 87

sulin rapidly and have too little left in the early morning hours to cause hypoglycemia. The table below shows six of these cases, with the CH distribution and blood sugars.

Two of these patients showed satisfactory control when the total carbohydrate was divided into three equal parts; the others required progressively larger feedings at lunch and dinner.

I give these examples to show how patients can be stabilized at a normal blood sugar level on *one dose* of protamine insulin daily, *provided the optimal carbohydrate distribution is determined individually for each case.* We have had many other equally satisfactory examples, but I do not wish to imply that results in all cases are as successful as these. The unstable cases, those with complications, and those who cooperate poorly are more difficult to keep well regulated, but this

is equally true with the other types of insulin and with any scheme of management.

The *advantages of protamine insulin* are: regulation with a single daily dose; greater latitude in the timing of the dose, for it makes little difference whether the injection is taken before or after breakfast, or an hour earlier or later; and greater latitude in the timing of the meals, so long as the fasting interval is not allowed to become too long. These are important advantages for the average patient and make it possible for him to live more normally.

Its *disadvantages* are, for some patients, the small breakfast and the bedtime feeding, and a certain loss of flexibility due to the relatively large carry-over from one day to the next, as a result of which the full effect of a change in dosage is only manifest after two or even three days. This tends to lengthen the time required for regulation and means longer hospitalization. It also makes it more difficult to handle patients whose food intake or carbohydrate tolerance may vary from day to day, as in surgical complications, infections and gastro-intestinal disturbances. Apart from these conditions, there are few diabetics who cannot be regulated on protamine to their advantage.

While hospitalization is desirable for accurate regulation, it is often possible in office practice to change the milder type of diabetic to protamine without hospitalization, if he will keep a careful record of the four daily urine specimens. When regulation appears to be satisfactory a fasting blood sugar should be done; this will serve as a guide to the amount of carbohydrate given at the bedtime feeding. Other blood sugars, before lunch and in the late afternoon, will confirm the correctness of carbohydrate distribution.

Globin Insulin.—We have been given the opportunity to study this preparation[8, 9, 10] through the courtesy of the experimental research laboratories of Burroughs Wellcome & Co., by whom it has been prepared. It is a combination of insulin with purified beef globin, which forms an insoluble suspension, analogous to the protamine insulin suspension. While it may be used in this form, acidification with dilute HCl to a *p*H of 4 or less causes it to form a clear solution which is more stable and easier to use. Optimum flocculation occurs at *p*H 6.1; at

pH 7.1 a preparation containing 40 units of insulin per cubic centimeter showed 13.1 units in solution at 25° C.

The globin insulin combination is less soluble in serum than protamine insulin, and the globin appears not to interact with serum protein as does protamine. The disintegration of globin insulin after injection appears to be a simple liberation of the insulin from a relatively insoluble combination with globin.

Blood sugar curves taken after the injection of globin insulin show a more rapid effect during the first two or three hours than after protamine insulin. This is followed by a period of prolonged hypoglycemic effect, about equal in intensity to that of protamine insulin, but of shorter duration, being practically ended within twenty-four hours. The duration of action is increased somewhat by the addition of a small amount of zinc to the preparation, as with protamine, but the preparations we have used have shown no perceptible carry-over beyond the twenty-four-hour period.

These characteristics endow the preparation with certain *clinical advantages:* The rapid development of action upon blood sugar makes it unnecessary to depend upon a carry-over effect from the previous day's dose to control blood sugar during the morning hours. The duration of effect is adequate to take care of an evening meal relatively high in carbohydrate, with sufficient control of the blood sugar level through the night. The diminishing effect during the night, however, makes it unnecessary to resort to bedtime feedings to prevent hypoglycemia in the early morning hours.

Absence of carryover facilitates the change from regular insulin to retarded insulin, since the entire dose is effective on the first day. It is not necessary to use a supplementary dose of regular insulin the first day or two, as with protamine, to compensate for the absence of carry-over. For the same reason it is unnecessary to wait two or three days after each change of dose for the development of its full effect. Regulation of the patient is thus hastened and hospitalization shortened. The same considerations give this preparation advantages in the conditions referred to above, where carbohydrate tolerance or food intake is likely to vary from day to day.

And when in such cases it is desirable to shift to regular insulin, the change is less difficult to carry out.

For the ordinary well-regulated, stable diabetic, the *advantages* of this preparation are in the more normal distribution of carbohydrate which it permits. Instead of four feedings, *only three* are required. The breakfast carbohydrate quota of 30 to 40 gm. of carbohydrate, slightly more than the average with protamine, accords well with the average patient's normal habits. The remaining carbohydrate is divided approximately equally between lunch and dinner in most cases. Some patients require a little more at lunch than at dinnertime, others the opposite. As with protamine, globin insulin permits considerable latitude in the time of the injection and of the meals.

Individual variations in the rate of response appear to be about the same as with protamine or regular insulin, patients who react slowly to one tending to react similarly to the others.

An important consideration in the use of retarded insulins is the question of *regularity* in the rate of absorption and action from day to day. Protamine insulin is highly satisfactory in this respect. While globin insulin appears to be equally constant in rate of absorption and action, we have not yet had a sufficient number of cases with repeated blood-sugar curves to be certain of this point, and it will have to be established by further observation.

The following cases regulated on globin insulin show the CH distribution required with this preparation, as compared with regular insulin and protamine insulin. All patients were hospitalized throughout the period of observation.

CASES ILLUSTRATING EFFECTS OF GLOBIN INSULIN

Case 1.—Diabetes of moderate severity in a middle-aged male, regulated first on protamine insulin, then on globin insulin suspension.

7/17/38: Stabilized for 12 weeks on:

         DIET   C200   P83   F100
         PZI   32-0-0
         CH DISTRIBUTION   30-60-70-40
         A.C. BLOOD SUGARS   78-148-143-111
       Changed to globin insulin, carbohydrate distribution altered.

7/25: GI   32-0-0 (7th day)
CH DISTRIBUTION   71-66-66-0
A.C. BLOOD SUGARS   129-236-160-114
The breakfast is too large, as shown by the blood sugar at lunch time.

7/28: CH DISTRIBUTION   60-71-71-0
A.C. BLOOD SUGARS   94-200-111-119
Breakfast is still too large.

8/5: CH DISTRIBUTION   50-80-70-0
A.C. BLOOD SUGARS   105-145-145-114

Regulation now satisfactory. Note larger breakfast and lunch and absence of bedtime feeding, as compared with PZI, with same effect on blood sugar.

The *suspension* of globin insulin has a relatively strong hypoglycemic effect during the morning hours and permits a relatively large breakfast. The *solution* is somewhat less active at this time of the day, but is slightly more active than protamine, as shown by the following cases, in all of which the *clear solution* of globin insulin was used.

Case 2.—Illustrating carbohydrate distribution on protamine zinc insulin and globin insulin.

3/15/39: PZI   55-0-0 for 3½ weeks:
DIET   C156   PS2   F82
CH DISTRIBUTION   31-34-66-26
A.C. BLOOD SUGARS   40-108-66-99
The low blood sugar before breakfast calls for a larger bedtime feeding; *the rise from breakfast to lunch calls for a smaller breakfast;* the drop from lunch to supper for a larger lunch, and the rise from supper to bedtime for a smaller supper. The low level of the curve calls for a reduction in the dose.

3/17: Changed to:
PZI   48-0-0
CH DISTRIBUTION   25-40-55-35
4/5: A.C. BLOOD SUGARS   84-87-95-100
Regulation excellent.

4/8: Changed to:
GI   48-0-0
CH DISTRIBUTION   40-60-55-0
4/12: A.C. BLOOD SUGARS   60-121-121-65
Hypoglycemia before breakfast and at bedtime.

5/1:   CH DISTRIBUTION   30-60-65-0
                  A.C. BLOOD SUGARS   *133-133-154-111*

             Regulation now satisfactory. The globin insulin permitted 5 gm. more carbohydrate at breakfast, 20 more at lunch, 10 more at dinner, and elimination of the bedtime feeding.

Case 3.—Comparison between protamine zinc insulin and globin insulin.
             DIET   C150   P60   F72 throughout.

4/12/39:   PZI   40-0-0
            CH DISTRIBUTION   30-40-50-30
            A.C. BLOOD SUGARS   90-114-93-85

            Typical carbohydrate distribution required for a flat blood sugar on PZI. Changed to GI; CH distribution altered.

4/21:   GI   40-0-0
            CH DISTRIBUTION   30-55-65-0
            A.C. BLOOD SUGARS   100-111-80-143

4/26:   *CH DISTRIBUTION   30-60-60-0*
            A.C. BLOOD SUGARS   *125-119-80-125*

            Regulation excellent; breakfast the same as with PZI, 20 gm. more CH at lunch, 10 more at dinner, elimination of bedtime feeding.

Case 4.—A male diabetic with high insulin requirement. This case illustrates the rapid gain in tolerance when regulated at a normal blood sugar level.

7/8/39:   *DIET   C150   P100   F70*
            PZI   105-0-0 (5th day)
            CH DISTRIBUTION   30-40-50-30
            A.C. BLOOD SUGARS   *77-87-74-91*

7/18:   DIET unchanged
            PZI   90-0-0 (8th day)
            A.C. BLOOD SUGARS   100-148-86-98

            Regulation satisfactory. Insulin requirement decreasing.

7/30:   DIET   C150   P120   F120
            GI   70-0-0 (4th day)
            CH DISTRIBUTION   36-60-54-0
            A.C. BLOOD SUGARS   *148-100-114-121*

            Satisfactory regulation with 6 gm. more CH at breakfast, 20 more at lunch, 4 more at supper, and elimination of the bedtime feeding. Marked reduction in insulin requirement.

Case 5.—An elderly woman, first stabilized on regular insulin, then shifted to globin insulin. DIET   C150   P60   F72 throughout.

3/15/39:   RI   20-0-20 for 5 days.
            CH DISTRIBUTION   50-50-50-0
            A.C. BLOOD SUGARS   114-59-100-73

            Blood sugar curve of typical form for regular insulin. Now shifted to globin insulin and CH distribution changed.

3/27:   GI   35-0-0 for 10 days.
        CH DISTRIBUTION   40-60-50-0
        A.C. BLOOD SUGARS   52-71-78-93
        The blood sugars are all low, despite the reduction of 5 units.

4/5:   GI   30-0-0 for 7 days.
        CH DISTRIBUTION   40-60-50-0
        A.C. BLOOD SUGARS   91-61-45-69
        Blood sugars still too low.

4/12:   GI   25-0-0 for 6 days.
        CH DISTRIBUTION   40-60-50-0
        A.C. BLOOD SUGARS   80-148-103-129
        Regulation now satisfactory; insulin requirement reduced from 40 to
        25 units.

Case 6.—An elderly male, stabilized first on regular insulin, then shifted to
    globin insulin. DIET   C180   P84-89   F72-76 throughout.

3/15:   RI   33-0-23 for 17 days.
        CH DISTRIBUTION   60-60-60-0
        A.C. BLOOD SUGARS   90-108-95-66
        Regulation satisfactory and stable. The form of the curve indicates
        somewhat delayed and prolonged action of the insulin.

3/27:   GI   50-0-0 for 10 days.
        CH DISTRIBUTION   50-70-60-0
        A.C. BLOOD SUGARS   74-143-80-70
        This curve calls for a reduction in the dose and for a smaller break-
        fast.

4/5:   GI   40-0-0 2nd day.
        CH DISTRIBUTION   40-80-60-0
        A.C. BLOOD SUGARS   78-89-69-28
        CH tolerance is increasing and the dose must be further reduced;
        shocks during evening; slightly delayed action.

4/12:   GI   27-0-0 2nd day.
        CH DISTRIBUTION   35-70-75-0
        A.C. BLOOD SUGARS   66-108-88-108
        Increase in the supper has brought up the bedtime sugar but is not
        yet enough to prevent morning hypoglycemia. Tolerance increasing;
        gradual reduction in dose to

5/31:   GI   15-0-0
        CH DISTRIBUTION   30-70-80-0
        A.C. BLOOD SUGARS   100-133-138-77
        Regulation excellent, with a marked improvement in CH tolerance
        after shifting to a slow-acting insulin, although previously stabilized
        at a normal blood sugar level on regular insulin.

Case 7.—Diabetes of moderate severity. Comparison of globin insulin with regular insulin.

4/5/39: DIET C150 P60 F72
RI 18-0-12
CH DISTRIBUTION 50-50-50-0
A.C. BLOOD SUGARS 95-167-154-190
Dosage inadequate.

4/17: Same diet.
GI 32-0-0
CH DISTRIBUTION 40-60-50-0
A.C. BLOOD SUGARS 77-167-105-180
Dosage still inadequate, as shown by high bedtime sugar, and breakfast too large.

4/21: DIET C141 P56 F70
GI 38-0-0
CH DISTRIBUTION 31-70-40-0
A.C. BLOOD SUGARS 80-129-138-133
Satisfactory regulation required a larger lunch and smaller supper than the average case, the insulin tending to act most strongly during the afternoon.

Case 8.—An elderly woman with an old hemiplegia and a 4+ Wassermann which had become negative after antiluetic treatment. She has developed a marked insensitiveness to insulin during the past year. Previously well controlled on about 70 units of PZI daily, she now shows 4+ glycosuria in all specimens and is finally controlled only when the dose is raised to 300 units daily.

6/12/39: DIET C150 P73 F78
PZI 260-0-0 (4th day)
CH DISTRIBUTION 25-45-55-25
A.C. BLOOD SUGARS 121-182-200-143

7/18: DIET C150 P80 F95
PZI 300-0-0 (4th day)
CH DISTRIBUTION 25-45-55-25
A.C. BLOOD SUGARS 112-108-114-121
Note the increase of 40 units required for a relatively slight effect upon the blood sugar level. Regulation now satisfactory.

7/30: Same diet.
GI 240-0-0 (11th day)
CH DISTRIBUTION 30-60-60-0
A.C. BLOOD SUGARS 72-114-85-75
Insulin requirement decreasing, after bringing blood sugar down to normal level. The extremely high insulin requirement in this case had no effect upon the pattern of CH distribution or on the ability to control blood sugars with one daily dose of slow-acting insulin.

Case 9.—A 68-year-old white female with severe diabetes. Regulation on regular insulin, globin insulin, and protamine insulin for comparison of effect. Repeated curves on globin insulin to study constancy of effect.

4/26/39:   DIET   C120   P64   F64
          RI   45-0-35
          CH DISTRIBUTION   40-40-40-0
          A.C. BLOOD SUGARS   103-160-103-100
          Changed to GI and CH distribution altered.

5/10:   GI   65-0-0 (5th day)
          CH DISTRIBUTION   30-50-40-0
          A.C. BLOOD SUGARS   77-131-148-167
          Rising blood sugars in evening indicate inadequate dosage. No change made in diet.

5/17:   GI   70-0-0 (6th day)
          A.C. BLOOD SUGARS   64-130-105-125
          Control now good.

5/23:   GI   70-0-0 (12th day)
          A.C. BLOOD SUGARS   74-110-140-114

5/31:   GI   70-0-0 (20th day)
          A.C. BLOOD SUGARS   80-128-133-76
          The last three curves were done under identical conditions, as a check on the regularity of response to GI. The values obtained are well within the range of variation to be expected under clinical conditions and would indicate that the preparation is satisfactory in this respect. She was now changed to PZI.

6/12:   DIET   C119   P71   F78
          PZI   70-0-0 (6th day)
          CH DISTRIBUTION   24-29-40-26
          A.C. BLOOD SUGARS   100-110-108-100
          A perfect blood sugar curve on protamine insulin at the same dosage level, but requiring 6 gm. less CH at breakfast and 21 gm. less at lunch, with 26 gm. given at bedtime.

Case 10.—The only case in which I have found it necessary to use regular insulin with protamine: a middle-aged woman highly insensitive to insulin, with practically no response to PZI during the morning hours. On 100 units of PZI and only 20 gm. of carbohydrate for breakfast the blood sugar rose from 132 before breakfast to 288 before lunch. When 20 units of RI were given with the protamine this rise was controlled.

3/30/39:   DIET   C130
          PZI   100 + RI 20
          CH DISTRIBUTION   20-30-30-50
          A.C. BLOOD SUGARS   114-138-160-116
          Changed to GI and CH distribution altered.

5/6:   GI   130-0-0 (suspension)
           CH DISTRIBUTION   44-42-42-0
           A.C. BLOOD SUGARS   166-114-110-126

Regulation good; the globin insulin suspension shows much stronger action during the morning, so that she now requires no regular insulin with the dose of retarded insulin.

Crystalline Zinc Insulin.—The addition of a small amount of zinc to a solution of pure insulin crystals tends to retard the action of the insulin upon the blood sugar. The effects of changing from regular insulin or protamine insulin to crystalline zinc insulin were studied in eight well-stabilized patients.

TABLE 1

BLOOD SUGARS AFTER REGULAR INSULIN AND AFTER CRYSTALLINE INSULIN IN THE FASTING DIABETIC

Patient.	Before insulin.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.
1. { R. I. 15 U......	112	95	83	54	57	57	57
{ C. I. 15 U......	118	118	118	83	72	50	63
2. { R. I. 15 U......	308	250	167	72	72	105	
{ C. I. 15 U......	308	286	160	105	72	35	32
3. { R. I. 15 U......	250	266	190	87	67	138	
{ C. I. 15 U......	334	282	210	168	125	95	54

Preliminary studies were first made in three cases (Table 1) to compare the course of the blood sugar in the fasting diabetic subject after 15 units of crystalline insulin and after 15 units of regular insulin. Initial blood sugar values ranged from 120 mg. to 334 mg. The results in all three cases showed after regular insulin a progressive fall in the blood sugar to a level between 50 and 100 mg., reached between the third and fourth hours. In two patients this was at once followed by a beginning rise; in the third patient the blood sugar value remained at a low level (57 mg.) from the third to the sixth hour, when the experiment was terminated. When crystalline insulin was used, the lowering of the blood sugar was retarded in all three cases, the maximum depression of the blood sugar being reached only at five to six hours, the lowest point being the same as, or a little below, that reached with regular insulin.

Similar curves were studied in the case of one patient after a breakfast containing 50 gm. of carbohydrate with 48 units of insulin (Table 2). Under these conditions there was less difference between the curves for regular insulin and crystalline insulin than in the fasting subject. The curves came together at the fourth hour and from that point on coincided, the maximum depression of the blood sugar being from the fifth to the sixth hour in both cases. In neither experiment was the blood sugar followed beyond the sixth hour, so that no information as to relative duration of effect was obtained.

TABLE 2

BLOOD SUGARS AFTER A 50 CH BREAKFAST, WITH 48 UNITS OF R. I. AND 48 UNITS OF C. I.

Patient.	Fasting.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.
4. R. I. 48 U. ..	168	132	123	100	118	85	78
C. I. 48 U......	173	185	160	154	111	80	75

The twenty-four-hour blood sugar curves in the eight cases studied showed what would be expected from these experiments. The diets in these cases ranged from 125 to 150 gm. of carbohydrate, divided into three equal portions; the insulin was given in two doses, before breakfast and before supper. The curves, in general, showed little significant difference. The data on three of these cases are given in Table 3. Whereas with regular insulin given according to this schedule the curve tends to drop from breakfast to lunch and rise from lunch to supper, with crystalline insulin the midday blood sugar tends to be a little higher than at breakfast and supper because of the retarded effect. Breakfast and supper levels were in general the same as with regular insulin.

We conclude from these studies that, *in the ordinary case, there is no significant difference between the behavior of regular insulin and crystalline insulin,* and that the *action of crystalline insulin is not sufficiently prolonged to permit satisfactory regulation with one dose daily.*

An exception was the case of a fourteen-year-old girl who was highly sensitive to insulin and highly unstable as regards insulin requirement from day to day. Like most of these pa-

tients she was most difficult to treat, since the violent fluctuations in the blood sugar level made it almost impossible to keep her free at the same time from glycosuria and from insulin reactions. In these cases a retarded insulin with prolonged steady action is often of great value. This child was stabilized as well as possible on regular insulin by using interval feedings after the breakfast and supper doses, with a small midnight dose to control the blood sugar during the latter half of the night.

TABLE 3

COMPARISON OF EFFECTS OF REGULAR INSULIN AND CRYSTALLINE ZINC INSULIN UPON THE BLOOD SUGAR OF PATIENTS

Patient.	Diet CH.	CH distribution.	Insulin.	Blood sugars, before		
				B.	L.	S.
1	150	50–50–50	R. I. 39–0–25	72	128	86
			C. I. 39–0–25 (3rd day)	66	125	90
			C. I. 39–0–25 (10th day)	69	107	85
			C. I. 39–0–25 (19th day)	60	112	90

Blood sugar curves identical after crystalline and regular insulin.

2	180	60–60–60	R. I. 60–0–15	88	80	114
			C. I. 60–0–15 (3rd day)	75	85	89
			R. I. 69–0–17 (13th day)	80	73	110

Crystalline insulin slightly less active at noon and slightly more active at supper time.

3	126	42–42–42	R. I. 10–0–5	114	85	125
			C. I. 10–0–5 (3rd day)	82	89	100
			C. I. 10–0–5 (6th day)	79	54	93
			R. I. 10–0–5 (8th day)	70	70	120

No significant difference between crystalline and regular insulin.

When crystalline insulin was substituted, it was found that the slower action demanded a radical change in the timing of the feedings and the insulin injections. To prevent afterbreakfast glycosuria it was necessary to give the insulin a full hour before breakfast and to reduce the breakfast carbohydrate. The midmorning feeding and the lunch had to be larger and the bedtime feeding had to be increased. On this program a fair degree of equilibrium was reached and she had only one slight shock during the following week, with irregular moderate glycosuria. She was then returned to regular insulin in the same dosage; heavy glycosuria recurred and the blood sugar level showed greater fluctuations. Evidently, in un-

stable patients of this type, *crystalline insulin may be definitely superior to regular insulin.*

Summary.—The examples given herein illustrate the methods used in regulating patients on the retarded insulins, and show the necessity for careful adjustment and timing of carbohydrate feedings if satisfactory control is to be achieved on one dose daily. They show, further, the importance of serial blood sugar observations as a check on control.

Protamine zinc insulin will control practically all diabetics on one daily dose, provided the optimal carbohydrate distribution is determined for each patient. Usually this requires a small breakfast and a bedtime feeding.

The inherently unstable diabetic with a variable insulin requirement from day to day is difficult to control with any type of insulin, but in the insulin-sensitive type it is usually easier to stabilize the blood sugar level with the slow-acting insulins.

A new globin insulin is described which acts more strongly than protamine upon the breakfast carbohydrate and which completes its action during the night with no perceptible carryover. It permits a larger breakfast than protamine and does not require a bedtime feeding.

Crystalline zinc insulin, while somewhat retarded and prolonged in action as compared with regular insulin, is not sufficiently long-acting to be capable of controlling blood sugar throughout the twenty-four hours with one dose daily.

BIBLIOGRAPHY

1. Joslin, E.: Protamine Zinc Insulin. Med. Clin. N. Amer., 22: 711 (May) 1938.

2. Lawrence, R. D.: The Treatment of Insulin Cases by One Daily Injection. Acta Med. Scandinav. supp., 90: 32, 1938; The Diabetic Life, London, J. and A. Churchill, 1937; Zinc Protamine Insulin in Diabetes. Treatment by One Daily Injection. Brit. Med. Jour., 1: 1077, 1939.

3. Pollack, H.: Dietary Suggestions for the Management of Diabetic Patients Using Protamine Zinc Insulin. J. Mt. Sinai Hosp., 4: 437 (Jan.-Feb.) 1938.

4. Boyd, J. D. and Jackson, R. L.: Levels of Control in the Treatment of Diabetes Mellitus. J.A.M.A., 111: 906 (Sept. 3) 1938.

5. Gray, P. A., Jr.: Discussion of Above Paper. J.A.M.A., 111: 909 (Sept. 3) 1938.

6. Neuhoff, F. and Rabinovitch, S.: Protamine Zinc Insulin. Arch. Int. Med., **62**: 447–460 (Sept.) 1938.

7. Mark, M. F.: Optimum Time for Administration of Protamine Zinc Insulin. Arch. Int. Med., **64**: 897 (Nov.) 1939.

8. Reiner, L., Searle, D. S. and Lang, E. H.: Proc. Soc. Exp. Biol. and Med., **40**: 171, 1939.

9. Bauman, L.: Clinical Experience with Globin Insulin. Proc. Soc. Exp. Biol. and Med., **40**: 170, 1939.

10. Bauman, L.: Clinical Experience with Globin Insulin. Am. Jour. Med. Sc., **198**: 475 (Oct.) 1939.

11. White, P. and Winterbottom, L.: Successful Treatment of Diabetic Girls with Protamine Zinc Insulin. J.A.M.A., **112**: 1440, 1939.

12. Pollack, H. and Dolger, H.: Advantages of Prozinsulin Therapy. Ann. Int. Med., **12**: 2010, 1939.

CLINIC OF DRS. JOSEPH WORTIS, KARL M. BOWMAN AND WALTER GOLDFARB

BELLEVUE PSYCHIATRIC HOSPITAL AND THE DEPARTMENT OF PSYCHIATRY, NEW YORK UNIVERSITY MEDICAL COLLEGE

THE USE OF INSULIN IN THE TREATMENT OF ALCOHOLISM

THE first effective use of insulin in the treatment of a psychiatric disorder was reported as early as 1926 by Edith Klemperer[1] in Vienna. Basing her treatment on the evidence of impaired liver function and diminished glucose tolerance in patients with delirium tremens, she concluded that their endogenous insulin production might be inadequate for the organism's needs, and accordingly treated a series of patients with moderate doses of insulin administered several times a day in combination with glucose. The value of this therapy was later confirmed by Auriat and Servantie,[2] Steck,[3] Gökay,[4] Puyuelo,[5] Säker,[6] Kral, Pollak and Schirmer,[7] Robinson,[8] and others. Recently a series of studies on the relationship of alcoholism to carbohydrate metabolism and on the therapeutic effects of insulin and glucose on certain alcoholic mental disorders were made at Bellevue Hospital and these will be briefly summarized at this time.

The Relationship of Alcoholic Psychoses to Alcohol. —It is impossible to relate the various alcoholic mental disorders to the direct toxic effect of alcohol, for in frank delirium tremens as well as in its subclinical form of "toxic" alcoholism, the alcohol has usually been metabolized or excreted long before the clinical symptoms subside. Even in the drunken state the relationship of the clinical symptoms to the level of blood alcohol is not by any means constant; the annoying "hangover" on the day following an alcoholic excess affords a familiar example of the persistence of mental symp-

toms after the alcohol has disappeared.[9, 10] Blochin[11] demonstrated a diminution in brain oxidation in dogs and cats following alcoholization, and recent work[11a] of ours at Bellevue Hospital indicates that alcohol also diminishes brain oxidation in human subjects. *In vitro* experiments of Robertson and Stewart,[12] however, show no such effect, and these authors even report an increase of the rate of oxidation of alcoholized sliced brain tissue lasting an hour before the rate begins to drop. Inasmuch as recent work of Courtial[13] and of Lundsgaard[14] indicates that there is a preliminary breakdown of alcohol in the liver before the final stage of oxidation in the tissues, the rôle of these intermediary products of alcohol metabolism may prove to be significant. Pohlisch,[15] and more recently Kral, Pollak and Schirmer,[7] attach particular importance to the acetonemia of chronic alcoholics.

The Use of Sugar to Reduce Blood Alcohol.—The buffering effect of food on the headiness of alcohol was already well known to drinkers and gourmands when Mellanby,[16] in 1919, proved that the simultaneous ingestion of food reduced the level of blood alcohol. These observations were later confirmed by Southgate,[17] and in a different way by Haggard and Greenberg,[18] who found that the toxicity of a given dose of alcohol was influenced inversely by the concentration of sugar in the blood. In 1937 Carpenter[19, 20] established that the ingestion of glucose hastened the disappearance of alcohol from the expired air of human subjects. In 1938 two of us (Goldfarb and Bowman[21]) demonstrated that the oxidation of alcohol *in vitro* was facilitated by the addition of glucose to the solution, and later showed, with Parker,[22] that glucose had a similar effect on the blood alcohol of human subjects.

The Use of Insulin to Reduce Blood Alcohol.—There are numerous studies of the effect of insulin on the level of blood alcohol. As early as 1926 Suphiewski[23] established that an appropriate dose of insulin could double the rate of disappearance of alcohol from the blood of rabbits. Aoki,[24] in 1927, in the course of his studies on the physiologic production of alcohol in animals, observed that insulin injections regularly reduced the amount of alcohol present in the blood of hens. Galamini[25] in 1932 found that insulin reduced the toxicity of alcohol for rabbits. The value of insulin in reducing

blood alcohol was later confirmed by Widmark,[26] Bickel,[27] Siegmund and Flohr,[28] though it was denied by Fleming and Reynolds,[29] Böhmer,[30] Sebastionelli,[31] and more recently by Goldfarb, Bowman and Parker.[22] These apparently contradictory results may be attributed in part to differences in dosage and timing. L. A. Meyer[32] has shown in a recent careful report that a dose of 0.3 units per kg. injected simultaneously
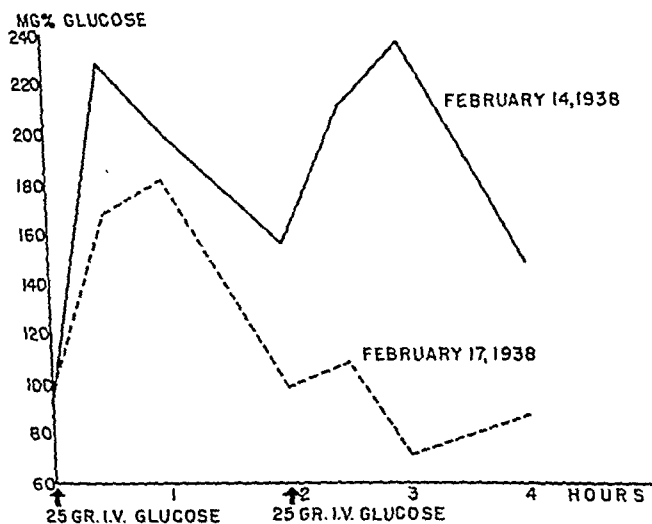
Fig. 78.—The impaired glucose tolerance of the "toxic" alcoholic: This patient (P. K.) was admitted to the insulin ward on Feb. 14, 1938, after a ten-day alcoholic bout, during which he ate very little. On admission he was tremulous, fearful, confused and restless, and experienced visual hallucinations. His blood sugar curve following intravenous injection of 25 gm. of glucose, repeated at the end of two hours, is shown by the solid line. The broken line shows the curve three days later when all the acute symptoms had spontaneously subsided. This patient had not been given the insulin-glucose treatment.

with the ingestion of alcohol generally reduces alcoholemia by about 15 per cent and also relieves the symptoms of acute, alcoholic intoxication.

The Impaired Glucose Tolerance of the Alcoholic.— Long before the discovery of insulin the glycosuria of certain psychotic subjects was a common topic of discussion in psychiatric literature. Arndt,[33] in 1897, reported the tendency to

glycosuria of patients with delirium tremens and reviewed much of the older literature in 1910.[34]   In 1901 Raimann[35] found a marked diminution of sugar tolerance in chronic alcoholics—as measured by the ease with which glycosuria could be induced—and observed that the sugar tolerance improved with the clinical improvement of his patients.   "Experience shows," he concluded, "that alcohol and alcoholism diminish sugar tolerance, but the disturbance disappears when the sub-
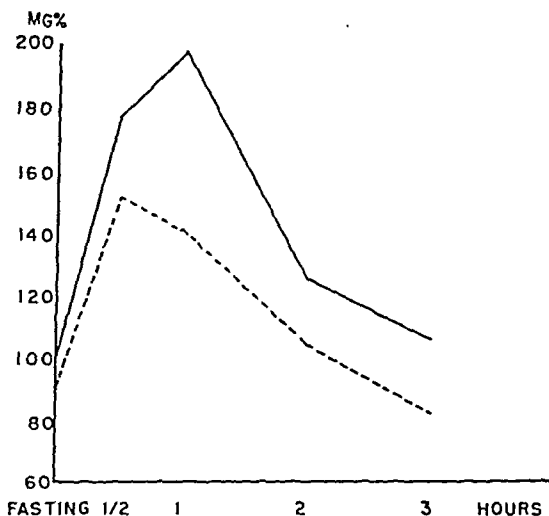
Fig. 79.—The impaired glucose tolerance of alcoholics: The solid line shows the course of the blood sugar curve after administration of 50 gm. of glucose by mouth in cases of "toxic" alcoholism with tremor and fearfulness (average of 9 cases). The dotted line shows the sugar tolerance curve of the same patients after spontaneous recovery one week later.

ject abstains from alcohol."   Other workers, using more refined technics, have substantiated this conclusion. Hétenyi,[36] in 1924, attributed the hyperglycemia of alcoholics to a direct toxic effect of alcohol on the tissues.   In 1926 Klemperer[1] remarked on the disturbed sugar tolerance of her patients with delirium tremens, and the impaired glucose tolerance of chronic alcoholics was already regarded as a well established fact by Pohlisch[14] at about the same time. In 1933 Gojcher, Weiland and Tarnopolskaja[37] also found a definite tendency to high glu-

cose tolerance curves in chronic alcoholics, and Rosendahl,[38] in 1935, confirmed these findings. Recently, Bowman, Wortis, Orenstein and Goldfarb[39] have again more fully substantiated Raimann's earlier observations on the correlation of glucose tolerance to the clinical condition of certain alcoholics. Typical sugar tolerance curves are shown in Figs. 78 and 79.

A number of factors probably contribute to this poor sugar tolerance of alcoholics: Alcohol is oxidized before glucose, even when both are available in the blood.[40] Since insulin is not necessary for the oxidation of alcohol, the endogenous production of insulin probably diminishes, as it does in subjects who have been fasting or who have been on a low carbohydrate diet. Moreover, subjects who have been on a protracted alcoholic bout have generally been eating too little in any case. And finally, the impaired liver function of chronic alcoholics probably retards the conversion of blood sugar to liver glycogen.

THE USE OF INSULIN AND GLUCOSE IN THE TREATMENT OF ALCOHOLISM

Since glucose provokes the release of insulin from the pancreas, and since insulin conversely provokes a mobilization of glucose from the liver, no sharp division can be drawn between the insulin and glucose treatments of alcoholism. In 1936 Kanitz[41] found that a combination of insulin and glucose generally reduced the alcoholemia in rabbits more effectively than insulin alone, and that the symptoms of drunkenness disappeared more rapidly even in cases where the alcoholemia was not influenced. In May, 1937, Kral, Pollak and Schirmer[7] reported good results with the insulin-glucose treatment of certain alcoholic psychoses as well as acute alcoholic intoxication, and recommended its use in acute alcoholism. The results in cases of alcoholic Korsakoff's psychosis were negative. Clark and Morrissey[42] demonstrated in 1938 that insulin and glucose in combination with alkalinizing salts accelerated the disappearance of blood alcohol in dogs. Säker,[6] in August, 1939, recommended insulin and glucose for improving the liver function of chronic alcoholics.

At Bellevue Hospital the insulin treatment was at first applied by Wortis, Bowman and Fingert[43] in the treatment of the

so-called toxic alcoholics. In February, 1938, a small series of such patients were treated on the insulin ward with moderate doses of insulin, though the administration of sugar was deferred as long as possible. It was noticed at that time, however, that these chronic alcoholic patients showed a marked sensitivity to even relatively small doses of insulin, and would show agitation or profound shock relatively soon after the injection, so that the hypoglycemia had to be terminated with glucose in an hour or two. Thirty units of insulin, for example, administered to a tremulous, sleepless and apprehensive alcoholic of average weight had a marked sedative

DAYS
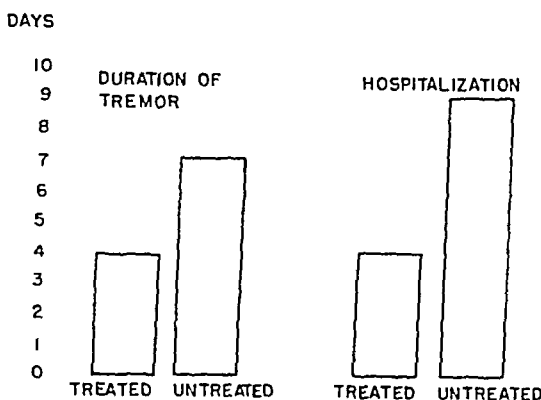
Fig. 80.—The results of insulin-glucose treatment in "toxic" alcoholism, as shown by duration of tremor and by length of hospitalization (average of 12 treated and 9 untreated cases).

effect within half an hour. In an hour or two the patients began to grow restless again and complained of hunger. At this point they were fed plentiful carbohydrates, after which they usually fell asleep or rested easily in bed. Their tremulousness and fearfulness were rapidly relieved and the benefits of treatment seemed unmistakable.

Our present practice is to administer the glucose solution by mouth within half an hour after the insulin injection, and to give the injections two or three times a day. In a recent series of cases so treated by the present authors, it was found that the speed of recovery could be approximately doubled in the treated cases (Fig. 80). It is noteworthy that there is

little or no alcohol present in the blood of such patients, but in a group of acutely alcoholic patients with high levels of blood alcohol, the insulin and glucose treatment has also been found by Goldfarb, Bowman and Parker[22] to be effective in diminishing the alcoholemia (Fig. 81). The drunkenness is rapidly relieved and an alcoholic stupor can be quickly broken by insulin and glucose administration. Though it is possible that the therapeutic mechanism is identical in both groups of cases, with the insulin attacking a by-product or intermediary
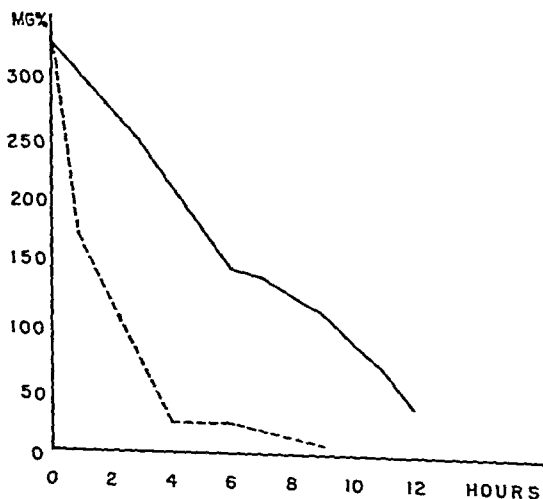
Fig. 81.—The effect of glucose and insulin administration on the blood alcohol level in humans (a typical case): The solid line represents the course of the blood alcohol level in an untreated patient. The dotted line represents the blood alcohol level in a second patient, with the same degree of alcoholemia, after the administration of 25 gm. of glucose and 15 units of insulin.

toxic product of alcohol metabolism rather than the alcohol itself, the problem requires further elucidation.

The Technic of Treatment.—Since alcoholics are particularly sensitive to hypoglycemia, presumably because their relatively small stores of liver glycogen prevent an adequate compensatory mobilization of glucose, *caution* is required in the management of the treatment.

With patients of moderate weight, we recommend a *dosage* of 10 to 25 units of insulin, administered two or three times daily, with a coverage of 200 to 300 cc. of 30 per cent glucose

solution administered by mouth within half an hour. Solid food should be taken within an hour to cover the additional insulin as it is absorbed.

The patients are encouraged at all times to sleep, rest and eat. An antiketogenic, high caloric diet, rich in vitamins and fruit juices, is desirable. The patients should be watched for signs of late shock, and any *excessively violent* reaction should be regarded as a sign of caution or as a contraindication to further treatment. Treatment in the late afternoon or evening should be avoided to prevent complications during the night, and the entire treatment should be administered *under the supervision of a physician or nurse.*

Treatment is continued until the patient recovers, which is usually a matter of one to several days. It will be found that sedation can usually be dispensed with once treatment is under way, but there is no reason why sedatives or other auxiliary drugs cannot be used as necessary.

For a more detailed account of other helpful measures the reader is referred to the paper on the treatment of delirium tremens recently published by the Bellevue Hospital group of workers.[44]

BIBLIOGRAPHY

1. Klemperer, E.: Behandlung des Delirium Tremens mit Insulin. Psychiat.-Neur. Wochenschr., 28: 549, 1926; Die Wirkung des Insulins beim Delirium Tremens. Monatschr. f. Psychiat., 74: 163, 1929; Die Behandlung des Säuferwahnsinns mit Insulin. Umschau., 37: 234–36, 1933.

2. Auriat, and Servantie, L.: Sur deux cas de délirium tremens traités par l'insuline. J. Med. Bordeaux, 58: 736, 1928.

3. Steck, H.: Die Behandlung des Delirium Tremens. Schweiz. Med. Wochnsch., 17: 68, 1936.

4. Gökay, F. Kerim: Gänzliches Verschwinden von Halluzinationen durch Insulinbehandlung bei einem Fall von Delirium Tremens. Psychiat.-Neur. Wochenschr., 38: 380 (August) 1936.

5. Puyuelo, E. Salinas: Fundamento de la Terapeútica Insulinica en el "Delirium Tremens." Siglo Méd., 96: 532 (Nov. 9) 1935.

6. Säker, G.: Zur Behandlung des Delirium Tremens. Nervenarzt, 12: 410 (August) 1939.

7. Kral, A., Pollak, J. and Schirmer, J.: Zur Insulinbehandlung der Alkoholpsychosen. (Read at the seventh congress of the Deutsche Gesellschaft für Innere Medizin und Neurologie in der Tschechoslowakischen Republik, May 9, 1937.) Nervenarzt, 10: 520, 1937.

8. Robinson, G. W., Jr.: Insulin Therapy in Acute Alcoholic Psychoses. J. Kansas M. Soc., 38: 463 (November) 1937.

9. Graf, Otto and Flake, E.: Zur Frage des Verlaufes der Alkoholblut-konzentration nach Alkoholgaben. Arbeitsphysiologie, 6: 141, 1932–33.

10. Graf, Otto: Über den Zusammenhang zwischen Alkoholblutkonzen-tration und psychischer Alkoholwirkung. Arbeitsphysiologie, 6: 169, 1932–33.

11. Blochin, N. N.: Die Wirkung von Äthylalkohol auf den Gaswechsel in verschiedenen Organen (nach Versuchen an angiostomierten Tieren). Ztsch. f. d. ges. Exper. Med., 98: 37, 1936.

11a. Goldfarb, W., Bowman, K. M. and Wortis, J.: The Effect of Alco-hol on Cerebral Metabolism. Am. J. Psychiat. (in press).

12. Robertson, J. D. and Stewart, C. P.: Effect of Alcohol on Oxygen Uptake of Brain Tissue. Biochem. J., 26: 65, 1932.

13. Courtial, Jean-Auguste: Recherches sur l'oxydation de l'alcohol éthylique dans l'organisme. Thèse de Paris, 1936.

14. Lundsgaard, Einar: The Pasteur-Meyerhof Reaction in Muscle Metab-olism. Harvey Lecture, Nov. 18, 1937.

15. Pohlisch, K.: Stoffwechseluntersuchungen beim chronischen Alkoholis-mus, Delirium Tremens und der alkoholischen Korsakow-psychose. Arch. f. Psychiat., 62: 211, 1927.

16. Mellanby, E.: Alcohol: Its Absorption into and Disappearance from the Blood under Different Conditions. Med. Research Comm. Special Report, Series No. 31, 1919.

17. Southgate, H. W.: The Effect of Alcohol under Varying Conditions of Diet, on Man and Animals, with Some Observations on the Fate of Alcohol in the Body. Biochem. J., 19: 739, 1925.

18. Haggard, H. W. and Greenberg, L. A.: The Effects of Alcohol as Influenced by Blood Sugar. Science, 95: 608 (June 25) 1937; Rate of Oxida-tion of Alcohol in the Body. J. Pharm. Exp. Ther., 52: 167, 1934.

19. Carpenter, Thorne Martin: The Metabolism of Alcohol in the Ani-mal Body. Scientific Monthly, 45: 5 (July) 1937.

20. Carpenter, Thorne Martin and Lee, R. C.: The Effect of Glucose on the Metabolism of Ethyl Alcohol in Man. J. Pharmacol. & Exper. Therap., 60: 264 (July) 1937.

21. Goldfarb, W. and Bowman, K. M.: The Effect of Glucose on the Oxidation of Alcohol in vitro. Proc. Soc. Exper. Biol. and Med., 39: 471, 1938.

22. Goldfarb, W., Bowman, K. M. and Parker, S.: The Treatment of Acute Alcoholism with Glucose and Insulin. Jour. of Clin. Investigation, 18: 581 (Sept.) 1939.

23. Supniewski, J. V.: The Influence of Insulin on the Acetaldehyde For-mation in the Body of Animals. J. Biol. Chem., 70: 13, 1926.

24. Aoki, J.: The Production of Alcohol in the Animal Body. Report III. Influence of Insulin on the Amount of Physiological Alcohol in the Blood of Animals. J. Biochem. (Japan), 7: 333, 1937.

25. Galamini: Arch. Farmacol. Sper., 45: 107, 1928; Bull. Acad. med. Roma, 58: 76, 1932.

26. Widmark, Erik M. P.: Der Einfluss der Nährungsbestandteile auf den Alkoholgehalt des Blutes. Biochem. Ztschr., 267: 135, 1933; Studien über den Einfluss verschiedener Nährungsbestandteile auf den Äthylalkoholgehalt des

solution administered by mouth within half an hour. Solid food should be taken within an hour to cover the additional insulin as it is absorbed.

The patients are encouraged at all times to sleep, rest and eat. An antiketogenic, high caloric diet, rich in vitamins and fruit juices, is desirable. The patients should be watched for signs of late shock, and any *excessively violent* reaction should be regarded as a sign of caution or as a contraindication to further treatment. Treatment in the late afternoon or evening should be avoided to prevent complications during the night, and the entire treatment should be administered *under the supervision of a physician or nurse*.

Treatment is continued until the patient recovers, which is usually a matter of one to several days. It will be found that sedation can usually be dispensed with once treatment is under way, but there is no reason why sedatives or other auxiliary drugs cannot be used as necessary.

For a more detailed account of other helpful measures the reader is referred to the paper on the treatment of delirium tremens recently published by the Bellevue Hospital group of workers.[44]

BIBLIOGRAPHY

1. Klemperer, E.: Behandlung des Delirium Tremens mit Insulin. Psychiat.-Neur. Wochenschr., 28: 549, 1926; Die Wirkung des Insulins beim Delirium Tremens. Monatschr. f. Psychiat., 74: 163, 1929; Die Behandlung des Säuferwahnsinns mit Insulin. Umschau., 37: 234–36, 1933.

2. Auriat, and Servantie, L.: Sur deux cas de délirium tremens traités par l'insuline. J. Méd. Bordeaux, 58: 736, 1928.

3. Steck, H.: Die Behandlung des Delirium Tremens. Schweiz. Med. Wochnsch., 17: 68, 1936.

4. Gökay, F. Kerim: Gänzliches Verschwinden von Halluzinationen durch Insulinbehandlung bei einem Fall von Delirium Tremens. Psychiat.-Neur. Wochenschr., 38: 380 (August) 1936.

5. Puyuelo, E. Salinas: Fundamento de la Terapeútica Insulínica en el "Delirium Tremens." Siglo Méd , 96: 532 (Nov. 9) 1935.

6. Säker, G.: Zur Behandlung des Delirium Tremens. Nervenarzt, 12: 410 (August) 1939.

7. Kral, A., Pollak, J. and Schirmer, J.: Zur Insulinbehandlung der Alkoholpsychosen. (Read at the seventh congress of the Deutsche Gesellschaft für Innere Medizin und Neurologie in der Tschechoslowakischen Republik, May 9, 1937.) Nervenarzt, 10: 520, 1937.

8. Robinson, G. W., Jr.: Insulin Therapy in Acute Alcoholic Psychoses. J. Kansas M. Soc., 38: 463 (November) 1937.

9. Graf, Otto and Flake, E.: Zur Frage des Verlaufes der Alkoholblut-konzentration nach Alkoholgaben. Arbeitsphysiologie, 6: 141, 1932–33.

10. Graf, Otto: Über den Zusammenhang zwischen Alkoholblutkonzentration und psychischer Alkoholwirkung. Arbeitsphysiologie, 6: 169, 1932–33.

11. Blochin, N. N.: Die Wirkung von Äthylalkohol auf den Gaswechsel in verschiedenen Organen (nach Versuchen an angiostomierten Tieren). Ztsch. f. d. ges. Exper. Med., 98: 37, 1936.

11a. Goldfarb, W., Bowman, K. M. and Wortis, J.: The Effect of Alcohol on Cerebral Metabolism. Am. J. Psychiat. (in press).

12. Robertson, J. D. and Stewart, C. P.: Effect of Alcohol on Oxygen Uptake of Brain Tissue. Biochem. J., 26: 65, 1932.

13. Courtial, Jean-Auguste: Recherches sur l'oxydation de l'alcohol éthylique dans l'organisme. Thèse de Paris, 1936.

14. Lundsgaard, Einar: The Pasteur-Meyerhof Reaction in Muscle Metabolism. Harvey Lecture, Nov. 18, 1937.

15. Pohlisch, K.: Stoffwechseluntersuchungen beim chronischen Alkoholismus, Delirium Tremens und der alkoholischen Korsakow-psychose. Arch. f. Psychiat., 62: 211, 1927.

16. Mellanby, E.: Alcohol: Its Absorption into and Disappearance from the Blood under Different Conditions. Med. Research Comm. Special Report, Series No. 31, 1919.

17. Southgate, H. W.: The Effect of Alcohol under Varying Conditions of Diet, on Man and Animals, with Some Observations on the Fate of Alcohol in the Body. Biochem. J., 19: 739, 1925.

18. Haggard, H. W. and Greenberg, L. A.: The Effects of Alcohol as Influenced by Blood Sugar. Science, 95: 608 (June 25) 1937; Rate of Oxidation of Alcohol in the Body. J. Pharm. Exp. Ther., 52: 167, 1934.

19. Carpenter, Thorne Martin: The Metabolism of Alcohol in the Animal Body. Scientific Monthly, 45: 5 (July) 1937.

20. Carpenter, Thorne Martin and Lee, R. C.: The Effect of Glucose on the Metabolism of Ethyl Alcohol in Man. J. Pharmacol. & Exper. Therap., 60: 264 (July) 1937.

21. Goldfarb, W. and Bowman, K. M.: The Effect of Glucose on the Oxidation of Alcohol in vitro. Proc. Soc. Exper. Biol. and Med., 39: 471, 1938.

22. Goldfarb, W., Bowman, K. M. and Parker, S.: The Treatment of Acute Alcoholism with Glucose and Insulin. Jour. of Clin. Investigation, 18: 581 (Sept.) 1939.

23. Supniewski, J. V.: The Influence of Insulin on the Acetaldehyde Formation in the Body of Animals. J. Biol. Chem., 70: 13, 1926.

24. Aoki, J.: The Production of Alcohol in the Animal Body. Report III. Influence of Insulin on the Amount of Physiological Alcohol in the Blood of Animals. J. Biochem. (Japan), 7: 333, 1937.

25. Galamini: Arch. Farmacol. Sper., 45: 107, 1928; Bull. Acad. med. Roma, 58: 76, 1932.

26. Widmark, Erik M. P.: Der Einfluss der Nährungsbestandteile auf den Alkoholgehalt des Blutes. Biochem. Ztschr., 267: 135, 1933; Studien über den Einfluss verschiedener Nährungsbestandteile auf den Äthylalkoholgehalt des

Blutes. Biochem. Ztschr., 270: 297, 1934; Hormonale Einflüsse auf den Alkoholumsatz. Biochem. Ztschr., 282: 79, 1935.

27. Bickel, A.: Biologische Wirkung des Alcohols auf den Stoffwechsel. Leipzig, 1936.

28. Siegmund, B. and Flohr, W.: Über den Einfluss von Insulin auf den Alkoholumsatz beim Menschen. Klin. Wchnschr., 16: 1718, 1937.

29. Fleming, R. and Reynolds, D.: Experimental Studies in Alcoholism: Attempts to Modify the Concentration of Alcohol in the Blood after Intravenous Administration of Alcohol. J. Pharmacol. and Exper. Therap., 54: 236, 1935.

30. Böhmer, K.: Die Einwirkung einige Arzneimittel auf den Verlauf der Blutalkholkurve. Deutsche Ztschr. f. d. ges. gerichtl. Med., 30: 205, 1938.

31. Sebastionelli, A.: Insulina ed alcoolemia provocata. Arch. per lo Stud. d. fisiopat. e clin. Ricambio., 6: 299 (July–Aug.) 1938; 6: 367 (Sept.–Oct.) 1938.

32. Meyer, L. A.: Untersuchungen über die Insulinwirkung auf die Blut-Alkoholkonzentration beim Menschen. Arch. f. Neurol. u. Psychiat., 43: 89, 1939.

33. Arndt, Max: Über Alimentäre und transitorische Glykosurie bei Behirnkrankheiten. Deutsche Zeitsch. f. Nervenheilk., 10: 419, 1897.

34. Arndt, Max: Über die Glykosurie der Alkoholdeliranten, Monatschr. f. Psych. u. Neur., 27: 222, 1910.

35. Raimann, Emil: Über Alimentäre Glykosurie. 2 Mittheilung: Glykosurie und Alimentäre Glykosurie bei Geisteskranken. Wien. klin. Wochenschr., 14: 512, 1901.

36. Hétenyi, Géza: Der Einfluss des Alkohols auf die Blutzuckerregulation. Zeit. f. d. ges. Exper. Med., 40: 261, 1924.

37. Gojcher, E. F., Weiland, W. and Tarnopolskaja, M. E.: Zur Frage der biochemischen Veränderungen bei chronischen Alkoholismus. Der Kohlehydratumsatz, die Alkalireserve, die Elektrolyten des Blutes. Acta Med. Scand., 79: 563, 1932–33.

38. Rosendahl, C.: Om Kullhydratomfintligheten hos Alkoholister Abs. in Zentralbl. f. d. ges. Neur. u. Psychiatrie, 77: 692, 1935; Med. Rev Bergen, 52: 214 (May) 1935.

39. Bowman, K. M., Wortis, J., Orenstein, L. and Goldfarb, W. The Sugar Tolerance of Alcoholic Patients. Proc. Soc. Exper. Biol and Med, 42: 37 (Oct.) 1939.

40. Tögel, O., Brezina, E. and Durig, A Über die kohlenhydratsparende Wirkung des Alkohols. Biochem. Zeitschr, 50: 296, 1913

41. Kanitz, H. R.: Über die Wirkung des Insulins auf den Verlauf der alimentärhyperglykämischen und alimentärhyperalkoholämischen Kurve. Arch f. Exper. Path., 183: 350, 1936.

42. Clark, B. A. and Morrissey, R W.: Influence of Insulin, Glucose and Alkalizing Salts on the Rate of Disappearance of Ethyl Alcohol from the Blood. Am. Jour. Physiol. (Proc.), 123: 37, 1938.

43. Wortis, J., Bowman, K. M and Fingert, H.: Unpublished data

44. Bowman, K. M., Wortis, H and Keiser, S : The Treatment of Delirium Tremens. J.A.M.A., 112: 1917, 1939.

ADDITIONAL REFERENCES

Blotner, H.: Alcohol Tolerance Tests in Normal Individuals and in Patients with Diabetes Mellitus and Diabetes Insipidus. New Eng. J. Med., 220: 283 (Feb. 16) 1939.

Brechmann, H. J.: Respirationsversuche nach Aufnahme von Fruchtzucker, Traubenzucker und Alkohol sowohl während der Ruhe als auch während der Arbeit. Ztschr. f. Biol., 86: 447, 1927.

Clark, B. B., Morrissey, R. W. and Fazekas, J. F.: Insulin and the Oxidation of Ethyl Alcohol by Excised Diabetic Liver Tissue. Science, 88: 285, 1938.

Dontcheff, L.: Influence des divers types d'aliments sur la vitesse d'oxydation de l'alcool éthylique chez l'homeotherme inanitié. Compt. Rend. Soc. de Biol., 126: 465, 1937.

Goldfarb, W. and Wortis, J.: The Availability of Ethyl Alcohol for Human Brain Oxidations (in press).

Hirschfelder, A. D. and Maxwell, H. C.: Effect of Insulin in Experimental Intoxication with Alcohol and Acetone. Am. J. Physiol., 70: 520, 1924.

Junge, K.: Zur Beeinflussung des Rauschzustandes durch Insulin in gerichtsärztlicher Beziehung. Dtsch. z. gericht. Med., 29: 1, 1937.

Mirsky, A. and Nelson, N.: The Influence of the Pancreas and the Liver on the Oxidation of Ethyl Alcohol. Am. J. Physiol., 127: 308, 1939.

Newman, N. W. and Cutting, W. C.: The Action of Dinitrophenol and Insulin in Accelerating the Metabolism of Ethyl Alcohol. J. Clin. Invest., 14: 945, 1935.

Nuzum, F. R. and Maner, G. D. Some Chemical Blood Changes in Chronic Alcoholism. J.A.M.A., 81: 456, 1923.

Schlichtung, H.: Experimentelle Untersuchungen über den Einfluss des Insulins auf den Verlauf der alimentärhyperglykämischen und hyperalkoholämischen Kurve. Ztschr. f. d. ges. Exper. Med., 97: 60, 1935.

Silvestri, G.: Alcoholismo e ormoni; influenza dell'adrenalina e dell' insulin sulla alcoolemia provocata. Arch. ital. di med. spr., 2: 633 (July) 1938.

Touvinen, P. F.: Über den Alkohol gehalt des Blutes unter Verschiedenen Bedingungen. Skand. Arch. f. Physiol., 60: 1–34, 1930.

CLINIC OF DR. Z. BERCOVITZ

FROM THE MEDICAL COLITIS CLINICS OF NEW YORK POST-
GRADUATE HOSPITAL AND SECOND MEDICAL (CORNELL)
DIVISION, BELLEVUE HOSPITAL AND THE DEPARTMENT
OF MEDICINE OF NEW YORK POST-GRADUATE MEDICAL
SCHOOL AND HOSPITAL AND THE DEPARTMENT OF MEDI-
CINE, CORNELL UNIVERSITY MEDICAL COLLEGE

RECENT ADVANCES IN THE TREATMENT OF CHRONIC ULCERATIVE COLITIS

MORE than ever before, the problems involved in the treatment of nonspecific chronic ulcerative colitis are attracting attention. Physicians who have had extensive experience with this type of patient recognize that the problem of treatment is greatly complicated by the fact that the etiology of the disease is still not known. Until it is possible to point to the causative factor or factors in chronic ulcerative colitis, therefore, the necessary preliminary to treatment must be a careful diagnosis and evaluation of all the known factors that enter into the picture in the disease.

With a view to learning more about the *etiology* of chronic ulcerative colitis, investigators have studied carefully the different factors that are related to the disease. They have conducted research into the bacteriologic aspects of chronic ulcerative colitis; into the importance of allergy, and the relationship of allergic manifestations to the disease; into associated mental and nervous factors; into vitamin and other definite deficiencies, which are thought by some to play an important part in the onset of the condition; and also into viruses as a possible causal factor. Some believe that primary invasion of the healthy bowel wall by organisms of bacillary dysentery is responsible for chronic ulcerative colitis; others blame the organism of amebic dysentery.

The results of these special lines of investigation tend to indicate that chronic ulcerative colitis is most probably not the result of any one of these factors alone. The inference, therefore, is that it is the result of systemic changes which are probably related to metabolic factors that are not known nor clearly understood at the present time. Thus it is of first importance for the clinician to remember that he is not treating bacteria, amebae, allergy, or viruses—he is treating a patient, and what he does for the patient, he does against the disease. In other words, it is probable that the deviations from normal observed in chronic ulcerative colitis are the result of systemic changes, and not *vice versa*.

The *periodicity* of chronic ulcerative colitis has frequently been observed. In some cases it tends to recur at the same season of the year; in others, it recurs in the same month. Moreover, it shows a very marked tendency to heal spontaneously. Relapses and recurrences seem to take place independently of, or in spite of, all treatment. The common cold or influenza is often the first debilitating illness from which the patient suffers, followed by chronic ulcerative colitis. Attacks of influenza may cause the recurrence of the disease.

Because chronic ulcerative colitis is debilitating, the patient needs a diet adequate in proteins and rich in vitamins. If there is any question of the patient's ability to absorb food, vitamins should be given in concentrated form, either orally or by injection. Routine treatment includes examination of the gastric juice for free hydrochloric acid and the administration of iron in some form and liver extract, either by mouth or by injection. As there is need for complete physical and mental rest, the patient suffering from chronic ulcerative colitis should be made to rest in bed. Other routine measures include blood transfusions, which should be given as frequently as necessary, and other supportive measures, such as glucose infusions. Methods of treating patients with chronic ulcerative colitis were summarized by the author and were presented by him at the Connecticut State Clinical Congress in September, 1939.

Criteria for the Evaluation of any New Method of Therapy.—It has been noted that the severity of the cases and the response to treatment vary with the individual and

with different months and seasons of the year. Consequently, a special form of therapy should not be attempted until these factors have been taken into account and until all routine treatment has been given. New methods of treatment are constantly being published, but their value must depend upon the success with which they have met the following *tests:*

1. The treatment of a large number of bona fide cases in which the diagnosis has been properly confirmed.

2. The observation of these patients over a sufficiently long period of time, before, during, and after treatment, to make certain that they do not belong to the type of patient who, with or without treatment, recovers spontaneously or who improves with the change of the season only to suffer a recurrence at the same time in the following year.

3. Carefully controlled observations on another group of patients extending over the same period of time and treated by other methods.

Experience has shown that *three years* is the minimum period for the accumulation of such data for the evaluation of any given therapeutic measure. It is not possible over a shorter period of time, even in the largest clinics, to see a sufficiently large number of bona fide cases of chronic ulcerative colitis to hazard a guess as to the real value of any given form of therapy. To be adequate, a period of five years should be allowed for the observation of patients because apparently successful new methods may not be able to withstand the test of time. Faith in those methods should therefore be qualified until they have been subjected to careful scrutiny for at least three, and preferably five, years even when early results give promise of brilliant success.

DIAGNOSIS

The symptom of *diarrhea* is, of course, of especial importance in the diagnosis of chronic ulcerative colitis. But what the patient may call "diarrhea" may not prove to be such. A patient may actually be constipated, but because he has seven or eight discharges a day of blood or mucus from the rectum he reports his symptoms as "diarrhea." One such case, on digital examination, was found to be lymphogran-

uloma venereum, with obstruction 4 cm. from the anus—a diagnosis which was confirmed by the Frei test (Fig. 82).

Thus it is important to remember that: (1) a patient may complain of diarrhea when in reality he is constipated and may even be suffering from an intensification of the constipation with definite narrowing of the bowel lumen; and (2) *digital examination* is a diagnostic procedure of vital importance, which should be followed by every physician and should be made a part of the routine diagnostic procedure in every case. It should also be remembered that a report of the presence of *Endamocba histolytica* in diarrheal discharges
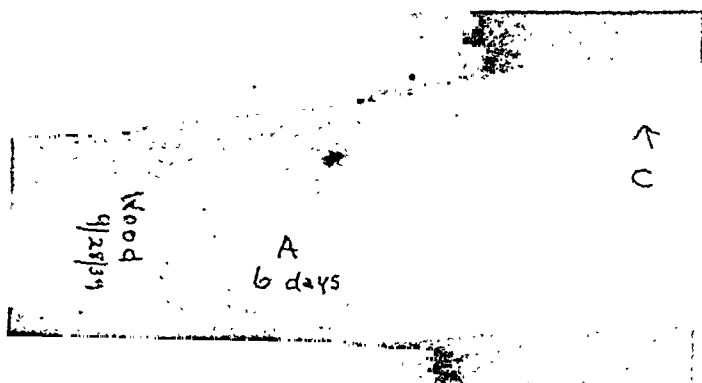
Fig. 82.—(Case I): Showing the Frei test as it appeared six days after the intradermal injection of Frei antigen (A) in mouse brain suspension. Note the control injection (C) has entirely disappeared.

of the patient should not be accepted as final unless or until typical forms of the ameba have been found. Heavy discharges of cellular exudate occur with chronic ulcerative colitis, and while the picture may be complicated by the presence of *Endamocba histolytica*, this complication should be confirmed before any specific diagnosis is made or treatment instituted.

Cellular Exudate Studies.—During the past four years the author has carried out extensive studies in the cellular exudates of bowel discharges in order to determine whether the presence or absence of cells has diagnostic significance. As a result of these studies, it has been established that the pres-

ence of cellular exudates in the bowel discharge indicates pathologic change in the bowel wall, whereas the absence of cellular exudates points to bowel conditions not associated with anatomic change.[1, 2, 3]

To study cellular exudates, the investigator should make a smear of the bowel discharge with Loeffler's methylene blue. A drop of the bowel discharge should be placed on a glass slide, thoroughly mixed with the methylene blue, and covered with a coverslip.

TYPES OF CELLS FOUND IN BOWEL DISCHARGES.—Two well-defined types of cell are found in bowel discharges:

1. *Polymorphonuclear Leukocytes.*—In methylene blue preparations, the nuclei of the polymorphonuclear leukocytes will be observed to be either solid, or else they may have open rings with beading of the nuclear membrane. Heavy granules of varying size and shape are found both within the nucleus and in the cytoplasm. It is also possible to determine whether the leukocytes are segmented or whether they are young forms. Whenever there is any suspicion that cysts of protozoa may be present in the specimen, Lugol's solution should be used to bring out the nuclear structure. The characteristic nuclear structure of the *Endamoeba histolytica* cyst differs completely from that of the polymorphonuclear leukocyte, and for that reason the examination with methylene blue and with Lugol's solution is of first importance in demonstrating the exact type of nuclear structure present.

2. *Epithelial Cells.*—Methylene blue preparations are the simplest to use for the observation of epithelial cells. These cells are of different sizes and shapes. Their nuclei are either round or oval, solid or ringed. In some cases, the nucleus resembles a solid mass when stained with methylene blue, while in others, it has the appearance of an open ring with fine beading and a central karyosome. The cytoplasm is usually smooth and finely granular, and it may or may not contain coarse masses of varying shapes.

LYMPHOGRANULOMA VENEREUM

In the past two years it has become an established practice to test patients having chronic ulcerative colitis with Frei antigen because cases of so-called "idiopathic" chronic ulcerative colitis have been discovered to be in reality cases of lymphogranuloma venereum. The antigen has been used in mouse brain suspension, and each test has been controlled by the use of the mouse brain suspension alone. The test with the control substance is necessary in every case to avoid the risk of false positive readings. Even when the control substances are used, it is difficult at times to decide whether or not the case is one of lymphogranuloma venereum. It is desirable, in every case, to make a tracing around the wheals formed both by the injection of the control substance and by the antigen, and to copy on tracing paper the rings marked around each of the wheals so as to secure a permanent record for reference purposes. The minimum time for reaction to the antigen is ninety-six hours, and no attempt should be made to evaluate the reaction before that period of time has elapsed. A positive reaction is given when a wheal or indurated area, with or without redness of at least 7 mm. in diameter, persists for at least four days after the injection of 0.1 cc. of antigen. There may be also papule and pustule formation at the site of the injection (Fig. 82).

Treatment of Lymphogranuloma Venereum.—As soon as a case has been positively diagnosed as lymphogranuloma venereum, intensive treatment with Frei antigen should be instituted. In our clinic, the Frei antigen made up in mouse brain suspension is used. Methods of administering the antigen vary in different clinics, but we have had excellent results by starting with 0.1 cc. subcutaneously every five days, increasing the dosage until the patient is receiving a total of 1 cc. of the antigen subcutaneously every five days. By this method, there are no severe systemic reactions, and improvement of the rectal condition, while slow and gradual, is very definite. We have not used the antigen intravenously because the results of the subcutaneous injections have been satisfactory. Cases have come to our attention in which the patient was suffering from almost complete rectal obstruction, and in which the desirability of surgical treatment was being consid-

ered. These cases have been treated with the Frei antigen only and, at the end of twelve months, we have been able to pass a full, standard-size ½ inch sigmoidoscope for its entire length without any difficulty. In the treatment of advanced cases of rectal involvement with lymphogranuloma venereum, the time factor is very important. These patients need treatment for a minimum of about one year, but they must be kept under observation for a considerably longer period.

Illustrative Case.—J. S., seen through the courtesy of Dr. William Sunderland of Danbury, Connecticut, had a history of symptoms of acute colitis of one month's duration. A biopsy of the rectum failed to indicate malignancy.

Fig. 83.   Fig. 84.

Figs. 83, 84.—J. S. Barium colon enema (Fig. 83) and cellular exudate studies in bowel discharges from patient with lymphogranuloma venereum and diffuse polyposis. Compare cells in Fig. 84 with those found in biopsy specimen (Figs. 87 and 88) and note predominance of small round cells with relative absence of polymorphonuclear leukocytes in both. Cellular exudate photomicrograph from preparation fixed in Schaudinn's fluid and stained with Heidenhain's iron-hematoxylin. (Oil immersion × 970.)

Later, sigmoidoscopy showed the rectum to be edematous and inflamed but not ulcerated. In the cellular exudate of the bowel discharge (Fig. 84), small round cells predominated and polymorphonuclear cells were conspicuously absent. The treatment given included the usual measures for nonspecific chronic ulcera-

Fig. 85.—External appearance of rectum five months after therapy with Frei antigen injections subcutaneously.

Fig. 86.—Biopsy specimen taken from rectum at onset at about the same time as exudate in bowel discharge shown in Fig. 84. Note, infiltration with round cells. H. & E. × 470.

tive colitis, as well as liver extract and a complete course of 50 histidine injections, which were ineffectual. Reexamination of the patient at the completion of the histidine injections showed that the rectum was filled with masses,

ranging up to 1.5 cm. long and 1 cm. wide, some of which protruded from the rectum, making digital examination difficult and instrumentation impossible. Examination of the bowel discharges showed the same cellular exudates as noted in Fig. 84. Then, because of the presence of the nodular masses and
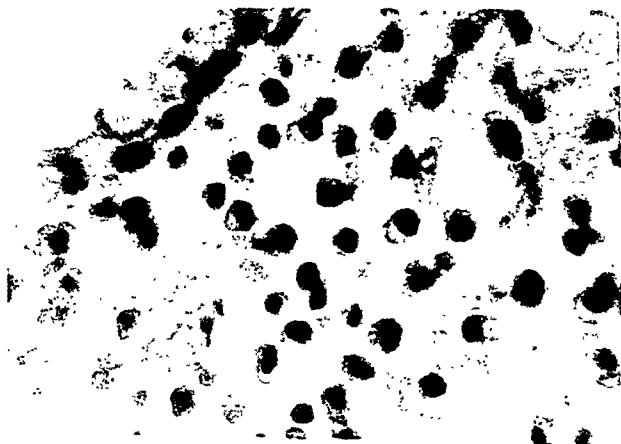
Fig. 87.
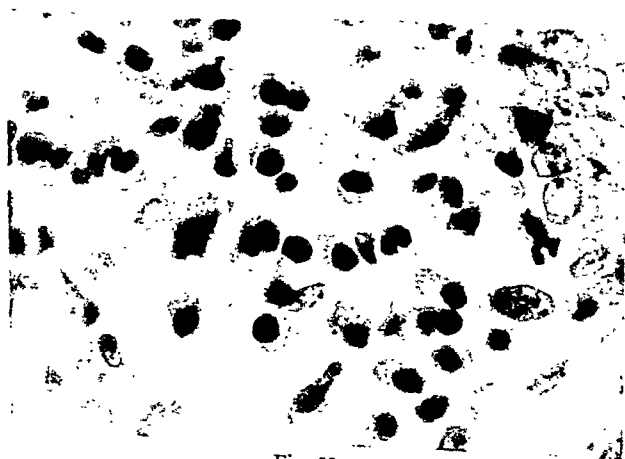
Fig. 88.

Figs. 87 and 88.—Oil immersion photomicrographs of two fields from Fig. 86. Note predominance of round cells over polymorphonuclear leukocytes and compare with Fig. 84. × 970.

the general appearance of the rectum, a Frei test was performed. This was strongly positive. A similar test on the patient's husband was even more strongly positive. Intestinal obstruction appeared imminent, and consequently
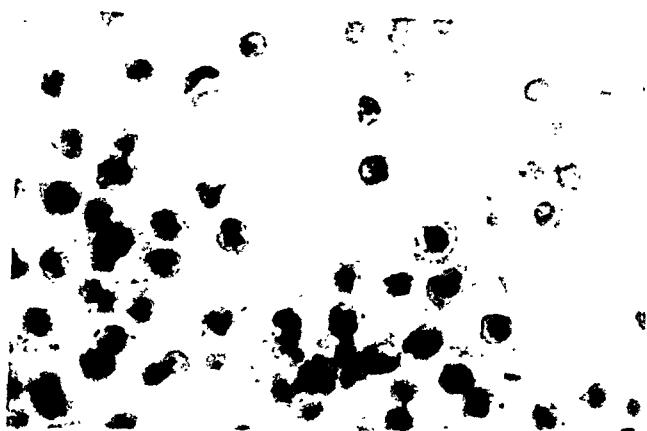
Fig. 89.—E. G., showing the results of cellular exudate studies in the case of a girl, sixteen years of age, who had had chronic ulcerative colitis for six years. (Courtesy of Dr. Irving S. Wright.) A and B, Note barium colon enema showing evidence of diffuse polyposis with chronic ulcerative colitis Sigmoidoscopy showed that the bowel wall was inflamed, bleeding, and ulcerated, and that there were numerous polypi in the field C, Shows the cellular exudate in the bowel discharge of this patient. This exudate is composed mainly of large, irregular-shaped cells with single, ringed nuclei A few polymorphonuclear cells only are present. When the patient began to improve during treatment, the cellular exudate diminished, and when she was clinically well, the cellular exudate disappeared entirely. While this patient had no

a colostomy was performed. At the time of the colostomy operation, it was noted that masses filled the rectum, sigmoid, and descending colon and, as a result, it was necessary to go over to the transverse colon before an area that was relatively free from polypi could be found. Even in that position the

A   B

Fig. 90.—Chronic ulcerative colitis of two years' duration with death following an acute exacerbation (which lasted only about a month). During this episode there was high fever, violent diarrhea and evidences of peritoneal irritation simulating acute peritonitis. Autopsy specimen of colon (A) showing large ulcers which were filled with pus. Cellular exudate (B) from bowel discharge showing polymorphonuclear leukocytes with ringed nuclei but not as large as those shown in Fig. 91. Cellular exudate photomicrograph from wet coverslip preparation in methylene blue. Oil immersion × 970.

polypi could be palpated with the examining finger within both the distal and proximal openings after completion of the operation. Barium, injected through the colostomy openings in the form of colonic enemas, showed evidence of diffuse polyposis (Fig. 83).

 Treatment was instituted with Frei antigen in increasing doses until the

symptoms of chronic ulcerative colitis, her stools were frequently examined and were invariably found to be free from cellular exudate. With the recurrence of symptoms, the cellular exudate again appeared and remained in the stools until the symptoms had completely abated once more. The study of stools for cellular exudates is of particular value in following the course of the diseased condition of the bowel wall. Cellular exudate photomicrograph from preparation fixed in Schaudinn's fluid and stained with Heidenhain's iron-hematoxylin. Oil immersion × 970.

A
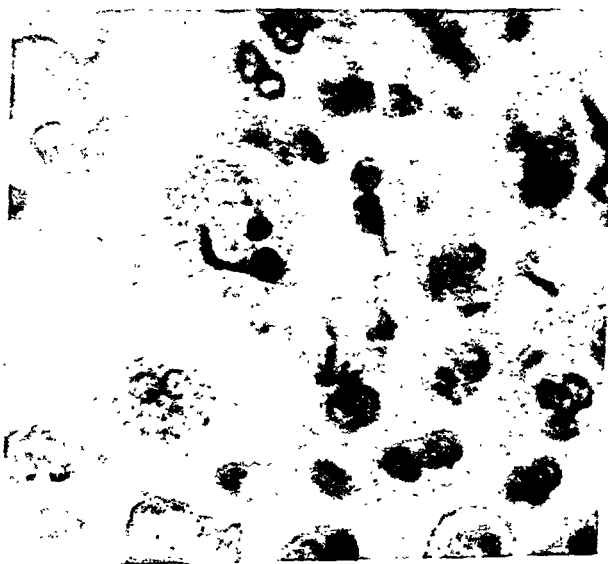
B

Fig. 91.

patient received 1.0 cc. of the Frei antigen in mouse brain suspension sub-
cutaneously every five days. At the end of five months, the patient was ex-
amined again and was found to have gained 30 pounds in weight. Digital
examination of the colostomy openings failed to reveal the presence of polypi,
and examination of the rectum showed that the masses, which previously had
made examination almost impossible, had disappeared. The external area had
the appearance shown in Fig. 85. Digital examination of the rectum showed
that it was relaxed, gaping, and funnel-shaped, and that it ended in a nar-
rowing about 4 cm. within the rectal sphincter. The wall had a few small,
shot-like masses, and at the area of obstruction there were many such masses,
the largest visualized being about 0.5 cm. Treatment with Frei antigen has.
been continued. The rectal discharge during the period of treatment has in-
creased, but this is typical of cases undergoing treatment with the antigen.

DEFICIENCY AND METABOLIC STATES IN CHRONIC ULCERATIVE COLITIS

One of the most recent advances in our approach to the
problem of chronic ulcerative colitis is in the recognition of
deficiency states associated with the disease. From the stand-
point of understanding the complex nature of chronic ulcera-
tive colitis, the fundamental problem is to determine if pos-
sible what metabolic or nutritional factors may underlie the
entire situation and may have existed for a long period of
time prior to the onset of the ulcerative colitis. The question
that has yet to be resolved is whether the circumstances which
seemed to cause the disease are incidental, or whether a fail-
ure over a considerable period of time of the metabolism of
food substances, including vitamins, carbohydrates, and pro-
teins, is responsible for the condition.

Vitamin Deficiency.—Deficiency frequently lies not in
the *quantity* of essential vitamins ingested, but in the *amount
absorbed* and *utilized* by the patient's system. The vitamin
deficiencies found in chronic ulcerative colitis include the en-
tire range of vitamins, and careful judgment has to be exer-
cised to determine the part each one plays in the whole body
complex.

Fig. 91.—Portion of colon removed at operation (A) and cellular exudate
(B) typical of that found at the onset of an acute toxic ulcerative lesion of
the bowel. Note the enlarged polymorphonuclear leukocytes with ringed nuclei
and a degenerated large cell (probably endothelial macrophage) with two
masses included. The course of this case was that of an acute fulminating
ulcerative colitis with death within one year of the onset. Cellular exudate
photomicrograph from methylene blue wet coverslip preparation. Oil immer-
sion × 970.

VITAMIN C.—In the past two years, two lines of investigation have been followed in respect to Vitamin C deficiency in cases of chronic ulcerative colitis. In one of these, tests were made to determine capillary fragility, following the method of Wright and Lilienfeld[4]; in the other, in cooperation with Drs. Wright and Ludden,[5] chemical studies were made of blood plasma levels, the saturation index of ascorbic acid, the loss of ascorbic acid in stools, the amount of ascorbic acid required to saturate the patient, and the daily ascorbic acid requirements necessary to maintain saturation.

The results of the first line of investigation, undertaken by Heineken and Bercovitz, showed that of thirty-two patients with chronic ulcerative colitis, twenty-seven (82 per cent) showed evidence of Vitamin C deficiency when given a capillary fragility test. Twenty patients have been observed for some time, and of them, ten had no bleeding after taking ascorbic acid, 300 mg. daily; seven were slightly improved; three showed no improvement with this method of treatment alone.

The findings of the second line of investigation are summarized as follows:

Pt.	Stools daily.	Vit. C. diet.	Plasma A. A.*, mg. %.	Saturat. index, mg.	A. A.* in stools, mg.	Oral A. A.* to saturate patient, mg.	Daily A. A.* requirement to maintain sat.	Course of colitis.
1	7–8	Fair	. . .	271	246 (24 hr.)	4400	200 mg.	Unimproved.
2	2–3	Fair	0.17	316	132 (6 hr.)	3600	150 mg.	Exacerbation with rhinitis.
3	3–4	Fair	0 22	374	20 (7 hr.)	2850	100 mg.	Unimproved.
4	7–8	Fair	0.24	337	. . . .	3400	175 mg.	Improved.
5	3–4	Good	0.78	716	19.2 (18 hr.)	.	. . . .	Improved.
6	2–8	Excel.	0 17	807	. . . .	.	. . .	Unchanged.
7	1–2	Good	0.50	544	. . . . .	.	7100 mg	Unchanged.
8	10–14	Good	0 24	. . . .	. . . .	6000	. .	Unchanged.
9	3–5	Good	0.65	545	. .	.	. . . . . .	Colectomy.
10	4+	Poor	0.10	98.0	1.5 (4 hr)	?	. . . . .	Unchanged.
Normal range			0.7–1.5	500–1000	2–16 (24 hr.)	1000–2000	50 10	

* A. A.: ascorbic acid.

1. Plasma levels in all patients without previous therapy were low although the dietary regimen in Vitamin C was fair.

2. In five patients with good diets and Vitamin C therapy, the plasma levels were good.

3. Saturation indices followed the plasma levels. This

method of approach to the problem is more satisfactory and accurate than capillary fragility studies alone.

4. The oral ascorbic acid requirements in ten patients with chronic ulcerative colitis is increased roughly in proportion to the number of stools and the amount lost in the stools.

5. Oral maintenance requirements ranged from 100 to 200 mg., given in divided doses daily to patients with chronic ulcerative colitis.

6. From 2000 to 6000 mg. are necessary to "saturate" such patients, depending upon the degree of deficiency, mode of administration, and other factors influencing the requirements.

7. Oral "test doses" depending upon urinary output are unsatisfactory in these cases.

The findings of these studies indicate that the Vitamin C intake of patients predisposed to Vitamin C deficiency should be increased to meet their minimum daily requirements. The patient should be *fully saturated* before the maintenance dose is given. Experience has shown that better results are obtained if Vitamin C is given in divided doses repeated at intervals, rather than in single large doses. This applies to both the saturation and maintenance doses. This method of administration takes into account the fact that Vitamin C is a kidney threshold substance (Wright and MacLenathen[6] and Wright[7]).

As a result of our experience, we cannot state that the course of the disease was conclusively affected by the administration of Vitamin C, although in a definite percentage of cases there was marked improvement of bleeding from the bowel following its administration. In the light of our present knowledge, a lack of Vitamin C cannot be considered an etiologic factor in chronic ulcerative colitis. It may be concerned with healing, and certainly it is concerned with the predisposition to capillary bleeding. Because it is a substance that can be determined with relative ease and accuracy, Vitamin C can be taken in general as an indicator of other deficiencies, some of which can be recognized and others of which we know nothing at the present time.

In the proper handling of chronic ulcerative colitis, Vitamin C should be administered in divided doses and in suf-

ficient amounts to be sure that the plasma saturation level is
maintained. When we begin treatment at the clinic, we give
as much as 300 mg. of ascorbic acid in a capsule, three times
daily. Then when the patient's capillary fragility tests show
that he has returned to normal and when his symptoms have
improved, we give 100 mg. three times daily as a maintenance
dose. When there is large loss of the vitamin through the
stool, it may be given intravenously or intramuscularly.
There are, of course, Vitamin C preparations which are de-
signed especially for these methods of administration.

GASTRIC DIGESTION.—It is more than mere coincidence
that we find in many cases of chronic ulcerative colitis, not
only low free hydrochloric acid values, but sometimes also de-
ficiencies sufficiently severe that they can be measured. Suf-
ficient hydrochloric acid and pepsin are necessary for the
digestion of proteins, which are the source of amino acids and
without which tissue growth and repair are seriously handi-
capped. It is often observed that most of the patients who
have Vitamin C deficiency also have a deficiency in hydro-
chloric acid. These patients exhibit a red, smooth, beefy
tongue. A common picture in chronic ulcerative colitis is that
of the patient (who complains of anorexia or even nausea and
vomiting) who exhibits the smooth, red, beefy tongue charac-
teristic of low or absent free hydrochloric acid in the gastric
contents and who has a definite Vitamin C deficiency. Doubt-
less these patients have also a marked Vitamin B deficiency.

Even when there is a certain amount of free hydrochloric
acid present in the gastric juices, the addition of hydrochloric
acid and pepsin to the regimen is definitely indicated because
it is not known at present just how much hydrochloric acid
is available three times daily for digestive purposes. Pepsin
is indicated as definitely as the hydrochloric acid. A helpful
prescription for this purpose is:

℞ Acid HCl (dilute)	30.0
Elixir lactus pepsin, q.s.	120.0
M. Sig.: 4 cc. t.i.d. pc in one-half glass of water.	

VITAMIN B AND LIVER EXTRACT.—For more than two
years liver extract by injection has been used as an adjunct in
the treatment of chronic ulcerative colitis in our clinic. We

admit frankly, however, that we do not know exactly what factors are involved in the improvement which we have noted in some of our patients. We believe that the use of liver extract may have been responsible for improvement in some cases and also for the maintenance in a relatively good condition in many others. The results have seemed better with the use of the simple concentrates of liver extract rather than with the more highly refined preparation. While many patients seem to improve with liver extract treatment, some do not, and some have remissions in spite of continued treatment. Liver extract has proved itself to be a valuable adjunct in the treatment of chronic ulcerative colitis, but it is in no sense a "cure" for the condition.

Histidine Hydrochloride.—The treatment of chronic ulcerative colitis with histidine hydrochloride began as an independent clinical investigation in September, 1936, in an effort to determine whether any demonstrable change would occur in the bowel mucosa as a result of the injection of the drug. It was thought that if the drug had a beneficial effect on the gastric mucosa, it should have a similar effect on the bowel mucosa. Although there was active discussion at that time regarding the value of histidine hydrochloride in the treatment of peptic ulcer, there was no record of its effect on the bowel mucosa. In favor of any investigation into the effect of the drug on the bowel mucosa was the fact that it would be a relatively simple matter to visualize the bowel wall at frequent intervals and thus to observe and record any changes that took place. This was a distinct advantage, because it had proved impossible to obtain direct objective evidence of the influence of histidine hydrochloride upon peptic ulcers because of the inaccessibility of the gastroduodenal mucosa to direct vision. Control injections of distilled water were given to some patients to discover whether any change would take place in the bowel mucosa as a result of such treatment. When enough injections were given to demonstrate the fact that there was no improvement in the condition, histidine hydrochloride was administered and the results of this treatment were observed.

The use of histidine has proved beneficial in a fairly high percentage of cases belonging to the category of nonspecific

ulcerative colitis that have been treated by Bercovitz and Fuller[8] in the past three years. To date, thirty patients have been treated by this method. Some patients have shown a remarkable response to this treatment, even some whose illness was of long duration. In every case the usual therapeutic measures, including vitamins, had been tried for periods of one to fourteen years before the histidine treatment was begun. Some members of this group have had no relapses in the three years; some showed improvement up to a point and then failed to make any further progress in spite of continued treatment. Others, who showed marked improvement with the first course of histidine, have had relapses. Histidine was helpful in some cases of relapse, but in others it made no contribution towards recovery. Treatment with histidine hydrochloride has failed completely in some cases.

The general impression gained of this method of treatment is that the results are sufficiently encouraging to warrant continuing it.

Blood Transfusions.—One of the most important recent advances in the treatment of chronic ulcerative colitis has been in the use of blood transfusions. Previously, blood transfusion was resorted to as a final measure of desperation; today, it is regarded as one of the chief methods of approach to the treatment of this disease.

Blood transfusions should be given early and in adequate amounts. It is not too much to give 500 cc. of blood every second or third day to a patient who is desperately ill with chronic ulcerative colitis. Blood transfusions of 500 cc. each can be given once a week to patients who are not so seriously ill. There is such a remarkable improvement in the general condition of patients who have been treated by this method that it is believed many lives have been saved. Blood transfusions are of particular value in cases of fever and frequent bowel movements, especially when these are attended with loss of blood. Either direct or indirect method of administration of the blood can be adopted according to the needs of the particular case and the preference of the physician.

Neoprontosil.—Considerable interest has been taken in the use of neoprontosil and other drugs of the sulfanilamide group in the treatment of chronic ulcerative colitis. The best

work in this field has been done by Bargen and his associates at the Mayo Clinic. The latest report of their work is published in the October, 1939, issue of the Annals of Internal Medicine. The results of neoprontosil treatment have varied; in some cases, remarkable results have followed while, in others, the results have not been as brilliant. They feel, however, that "the lack of toxic manifestations associated with the use of this drug and the comparatively encouraging clinical responses amply justify the use of neoprontosil (oral) in the treatment of chronic ulcerative colitis" (p. 713).

In the early days of sulfanilamide therapy we treated large numbers of patients with this drug. Our failure to obtain satisfactory results may be due to the fact that we did not use sufficiently large doses. But since the reports of Bargen[6] with neoprontosil, we are again seriously considering the use of this drug.

Foci of Infection in Chronic Ulcerative Colitis.— Careful attention must be given to the searching out and eradication of foci of infection. This is particularly important in the urinary tract. Patients with chronic ulcerative colitis frequently have urinary tract infections. In many cases, the only indication of such infection may be the presence of relatively few white blood corpuscles per high-power field in the urine examination. But failure of the patient to respond to treatment for the colitis may be due to the presence of urinary tract infection. Valuable information can be obtained by collecting each specimen of urine separately for a period of one or two days and examining each one immediately for the presence of pus cells.

Diet.—Patients with chronic ulcerative colitis should have a high protein and low residue diet, well balanced in vitamins. Enough starches should be added to maintain the patient's caloric requirements. Scraped chopped beef, either raw or rare, which may be given twice a day, is definitely indicated. It will be found that the patient's strength can be maintained better under this regimen than if gruels and starchy substances only are given. Red meat (beef) should be given when the tongue is smooth and glassy, the gums bleeding and spongy, when free hydrochloric acid is lacking, and when the patient is anemic. Milk should not be given, although buttermilk is

acceptable. Puréed vegetables are indicated, and the list should include green vegetables as well as baked potatoes. Gas-forming vegetables, such as onions, should be avoided.

All diets should be served in the most attractive manner possible. Small amounts will tempt the patient more readily than large portions. The patient with chronic ulcerative colitis is nauseated and certainly not hungry, and should therefore not be confronted with a large tray containing all kinds of foods. It is much better to serve one article of food alone. Most patients will be discouraged when given many things to eat, whereas they will attempt to eat the one item offered them.

SPECIAL DIET LIST

Important Note: Read and Follow Exactly

1. The object of this diet is to provide foods which will be easily digested, readily absorbed and leave a minimum of residue which might be irritating to the bowel.
2. Your absolute cooperation in the matter of diet is vital for the proper handling of your condition.
3. Make no changes without consultation. *Eat only the foods listed below.*
4. Please bring this diet list with you at each office visit.
5. Eat some of the following food at 10 a.m., 4 p.m., and at bed time: Bouillon, chocolate-flavored vitavose (Squibb), eggnog, fruit juice, Holland rusk, toasted white bread, zweibach.

Only the Foods Listed Below May Be Eaten:

Beverages—Bovril, cocoa, coffee, cream, milk, weak tea, vegex, vichy (fruit juices as listed).

Bread stuffs—Bread sticks, dry white toast, Holland rusk, melba toast, zweibach.

Cereals—Cream of wheat, farina, hominy, strained oatmeal.

Desserts—Cornstarch pudding, custards, D-zerto, ice cream (without nuts or seeds), jello junkets, Knox gelatin, Royal pudding.

Eggs—Poached, soft-boiled, scrambled in double boiler; or used in eggnogs or custards.

Fruits—Puréed or canned; grapefruit (canned or fresh without membrane), peaches, pears, bananas.

Fruit juice—Grapefruit juice, orange juice, pineapple juice, tomato juice.

Meats—Lean bacon, roast beef, scraped chopped beef, heart (calves, beef, lamb), lamb chops (broiled), roast lamb, filet of sole (broiled or boiled), boiled tongue, boiled ham and calves liver.

Soups—Bouillon, half milk and half cream with addition of puréed vegetables, strained vegetable soup in which no onion or other gas-forming vegetables have been cooked (made from only vegetables listed below), lentils and split pea.

Starches—Baked potato (without the skin), mashed or other soft forms of potato, rice (well cooked with plenty of water till soft), macaroni, and spaghetti.

Vegetables—All to be puréed: Asparagus, beets, beet greens, carrots, peas, spinach, squash, string beans, swiss chard, broccoli.

Do Not Take the Following:

Alcohol—No alcohol in any form.

Cathartics—No cathartics or laxatives in any form.

Meats—No cured meats; no fried meats; no corned beef, dried beef, ham, kidney, pork, shell fish, or veal.

Pastry—No rich pastries.

Spice—No highly spiced or highly seasoned foods.

Vegetables—No vegetable which has not been puréed; no artichoke, brussels sprouts, cabbage, cauliflower, corn, cucumbers, lettuce, lima beans, onions, peppers, radishes, sauerkraut, scallions, tomatoes, turnips, watercress.

Beverages—Alcohol must be eliminated in every case of chronic ulcerative colitis. Even medications containing alcohol prove injurious to the patient. Beverages may include tea, malted milk, or buttermilk.

It is often desirable to give the patient nourishment between meals. A nourishing drink may be made as follows: whip one tablespoonful of malted milk powder into about 3 or 4 ounces of water; beat in one or two eggs when the powder is thoroughly mixed, and serve with a scoop of vanilla ice cream. Another means of giving light nourishment is by adding 2 or 3 ounces of pressed beef juice to beef broth. This should be served either clear or else with some well cooked rice.

Tomato juice may be given with one meal. It should be taken with food, and not on an empty stomach. When served first of all, the patient should be given tablespoonful amounts, and these can be built up to 2 or 3 ounces with each meal. Many patients are able to do well with tomato juice when given in this way, whereas they could not manage it if given in a large quantity on an empty stomach. Orange juice is more likely to cause distress than tomato juice.

BIBLIOGRAPHY

1. Bercovitz, Z.: Studies on Cellular Exudates of Bowel Discharges I; Control observation in 1123 patients, 7 autopsies and 3 dog experiments. To be published in the Journal of Laboratory and Clinical Medicine.

2. Bercovitz, Z.: Studies on Cellular Exudates of Bowel Discharges II; The Differential Diagnosis of Amebiasis.—Types of Cells found in Bowel Discharges of Patients with Bowel Complaints. To be published in the American Journal of Digestive Diseases and Nutrition.

3. Bercovitz, Z.: Studies on Cellular Exudates of Bowel Discharges III; The Clinical Significance of Cellular Exudate Studies. To be published in the Annals of Internal Medicine.

4. Wright, I. S. and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid) with Especial Reference to its Effects on the Capillary Fragility. Arch. Int. Med., 57: 241–274 (Feb.) 1936.

5. Wright, Ludden and Bercovitz: Unpublished results.

6. Wright, I. S. and MacLenathen, E.: Vitamin C Saturation—Kidney Retention after an Intravenous Test Dose of Ascorbic Acid. Proc. of the Soc. for Exp. Biol. and Med., **38:** 55–59, 1938.

7. Wright, I. S.: The Present Status of the Clinical Use of Cevitamic Acid (Ascorbic Acid) (Crystalline Vitamin C). Amer. Jour. of Med., **192:** No. 5, p. 719 (Nov.) 1936.

8. Bercovitz, Z. and Fuller, C. C.: Unpublished results.

9. Brown, A. E., Herrell, W. E. and Bargen, J. A.: Neoprontosil (Oral) in the Treatment of Chronic Ulcerative Colitis. Ann. Int. Med., Vol. 13, No. 4, Oct., 1939.

CLINIC OF DRS. ALEXANDER S. WIENER* AND GEORGE SCHAEFER

SEROLOGICAL LABORATORY OF THE CHIEF MEDICAL EXAMINER OF NEW YORK CITY AND THE DEPARTMENTS OF SURGERY, GYNECOLOGY AND OBSTETRICS OF THE SEA VIEW HOSPITAL

LIMITATIONS IN THE USE OF PRESERVED BLOOD FOR TRANSFUSION

A STUDY OF THE FATE OF THE TRANSFUSED ERYTHROCYTES IN THE RECIPIENT'S CIRCULATION

ONE of the most important problems relating to the use of preserved blood for transfusions is the time limit for the storage of the blood. Concerning this very practical point there is no unanimity of opinion, expiration dates ranging from two to ninety days having been suggested by various authors.

Two methods for the solution of this problem suggest themselves: (1) to study the chemical and morphologic changes in blood stored for varying periods *in vitro*, (2) to ascertain the results of transfusions of preserved blood. Our own investigations did not include *in vitro* studies, but a review will be given later in this paper of published work along this line. With regard to the second method of approach, neither hemoglobin determinations nor clinical observation offers reliable criteria for the evaluation of the results of a transfusion. A more objective method is to trace the fate of the transfused erythrocyte in the patient's circulation.

While it is not possible, as a rule, to distinguish the bloods of two individuals of the same species by morphologic characteristics,* this can be done by serologic methods. This principle was first applied by Todd[3] to study the survival of transfused erythrocytes in cattle. In man, the method was first applied by Ashby[4] to patients of groups A, B, and AB who had been given transfusions from so-called universal donors (group O). Since most authorities prefer to transfuse only blood of the homologous group, there is some difficulty in applying Ashby's method as a routine. The existence of individual differences in human blood independent of the four blood groups, particularly the agglutinogens M and N of Landsteiner and Levine, makes it possible to trace transfused erythrocytes also in cases where the patient and donor belong to the same blood group. It is the purpose of the present study, with the aid of this serologic technic, to compare the survival time in the patient's circulation of blood stored for varying periods up to twenty-one days with that of fresh blood.

A number of studies have already been made on the duration of life of transfused fresh blood. Ashby[4] and Wearn, and Warren and Ames,[5] using universal donors, found that the donor's blood could be demonstrated in the patient's circulation for periods up to from 80 to 120 days. Using the agglutinogens M and N, Landsteiner, Levine and Janes[6]; Wiener[7]; and Dekkers,[8] have confirmed these estimates for the survival time of fresh blood. Only one report has come to our attention in which an attempt was made to apply either method to transfusions of stored blood. In this report by Perry[9] a case is described of a patient of group AB who was given a transfusion of group O blood that had been preserved for one week. Four weeks after the transfusion almost all the transfused cells could still be demonstrated in the patient's circulation by Ashby's method, and no attempt was made to follow the case further. No conclusion can be drawn from this single study as to the relative merits of fresh and preserved blood.

* Certain rare individuals, however, exhibit a hereditary anomaly of their erythrocytes in that these, instead of being round, are elliptical. This peculiarity in the shape of the erythrocytes was used for a study of the survival time of transfused blood cells by Huck and Bigelow.[1] For other studies along these lines see Wildegans.[2]

In the present study we shall analyze observations on the fate of transfused erythrocytes in twenty-eight patients receiving blood stored for periods ranging from three hours to twenty-one days. In addition there were thirty-two patients who could not be studied from this angle, either because patient and donor both belonged to the same M-N type, or because the patient was given repeated transfusions.

Materials and Methods.—All the cases to be discussed here were of patients in the wards of the Sea View Hospital. The great majority of them were given transfusions as a pre- or postoperative measure. Specimens of blood were taken from each patient immediately before and several hours after the transfusion, and thereafter, as a rule, at intervals of one or two weeks. In a few cases samples were collected at intervals of several hours during the first and second days following the transfusion. Duplicate samples were always taken, part in citrate solution and the remainder in a dry clean tube. The pretransfusion sample was used primarily for determining the group and type of the patient. The group and type of the donor were ascertained from samples of blood taken at the time of the phlebotomy. The typings were usually done on fresh bloods, but at times, not until after the transfusions had been given, namely, up to one to three weeks after the blood had been drawn. Despite the age of the blood and occasional pronounced hemolysis, the agglutination reactions were clean-cut and there was never any difficulty in determining the blood group or M-N type. On the other hand, the samples taken from the patient after the transfusion for the follow-up were always examined while perfectly fresh because of the delicate nature of the tests.

Naturally, the only cases that were followed were those in which patient and donor belonged to different M-N types. For these studies the same anti-M serum and anti-N serum were used throughout, these having been selected from a number of sera on account of their high potency and specificity. The antisera used in a given case depended, of course, on the combination of types of donor and patient. For example, where the patient belonged to type MN and the donor to type N, only the anti-M serum could be used for distinguishing the two sorts of blood. If we assume that following the usual 500 cc. transfusion about 10 per cent of the erythrocytes in the patient's circulation will have been derived from the donor, in this illustrative case there would be a mixture of 9 parts of MN blood to 1 part of N blood. Accordingly only nine tenths of the patient's cells will now agglutinate in the anti-M serum, whereas before the transfusion there had been complete agglutination. On the other hand if the patient belonged to type N and the donor to type MN, the situation would be reversed, only one tenth of the cells agglutinating in the anti-M serum after the transfusion.

In Fig. 92 the microscopic appearances of the agglutination reaction in the two illustrative cases cited above are given, and for comparison Fig. 93 is given in which are illustrated ordinary positive and negative agglutination reactions.
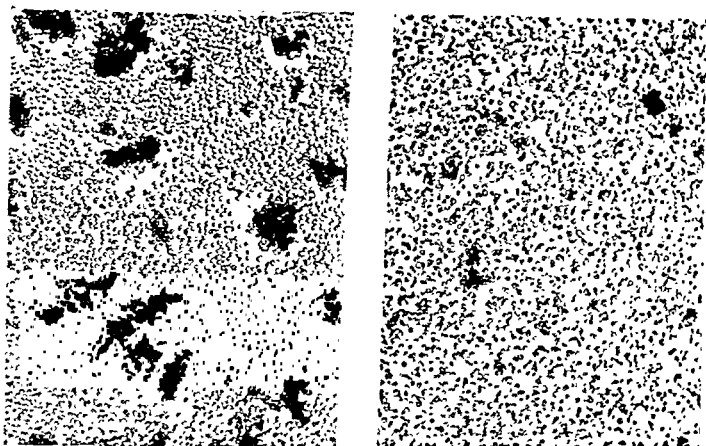
Fig. 92.—Agglutination reactions with anti-M serum following blood transfusions. *Left:* Patient type MN and donor type N. The agglutinated cells here are the patient's, the unagglutinated, the donor's. *Right:* Patient type N and donor type MN. Here the agglutinated cells are the donor's, the unagglutinated, the patient's.
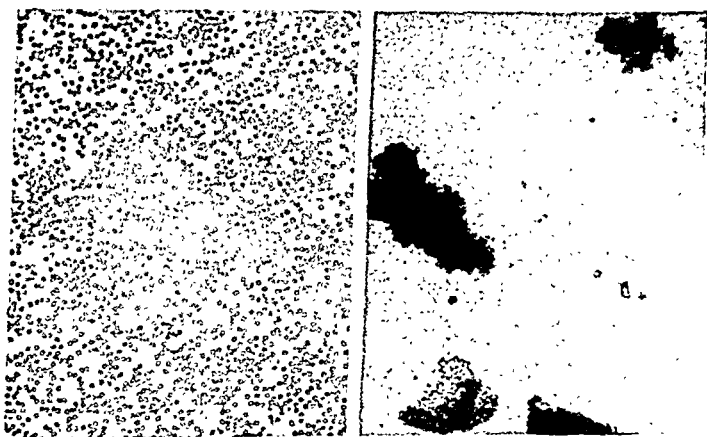
Fig. 93.—Microscopic appearance of typical agglutination tests. *Left:* Negative reaction—each red blood cell is separate and distinct. *Right:* Positive reaction—the red blood cells are agglutinated together in large clumps with only rare free cells. (Wiener's "Blood Groups and Blood Transfusion." C. C. Thomas, 1939.)

In instances where the patient belongs to type N and the donor to type M or vice versa, both the anti-M serum and the anti-N serum can be used, thus providing a double check on the results. In our series, there was one patient of group B, type M who was given group O, type N blood. In this particular case there was a triple check on the results, since three different sera could be used for recognizing the transfused erythrocytes, namely, anti-M, anti-N and anti-B.

The number of transfused erythrocytes remaining in the patient's circulation can be determined by a technic similar to that used for making ordinary red blood cell counts. For example, following a transfusion of type N blood to a type M or type MN patient, a sample of blood is taken from the finger into a red cell pipette, using anti-M testing fluid as the diluting fluid. The mixture is allowed to stand for one to two hours until agglutination is complete and then gently shaken. A drop of fluid is transferred to a counting chamber, avoiding clumps as much as possible. The unagglutinated cells, which are the donor's cells, can now be counted in the usual manner. This method was not used in the present study because it was not feasible to carry out such an elaborate technic routinely in a large number of cases. Besides, it was found that in the microscopic examination of the agglutination reactions of the follow-up blood samples, it was possible, with practice and particularly by comparison with artificial mixtures of known blood samples, to estimate fairly accurately the proportion of agglutinated cells to unagglutinated cells. For this purpose the entire specimen was examined under the low power microscope, since a single field, as illustrated in Fig. 92, may not accurately represent the true proportion between the two types of cells. Accordingly, this method was used for estimating the number of transfused cells in the patient's circulation. For the sake of simplicity in tabulating the results, the number of surviving transfused erythrocytes is expressed as a percentage of the original amount injected. Although the estimates obtained were crude, so that at times there were gross fluctuations in the counts from week to week, the method served satisfactorily for the present study and the end-point, that is, the time when all the transfused blood had been eliminated from the patient's circulation, could always be reliably determined.

Since the method of collecting and storing the blood for transfusion may have some influence on the results obtained, we include a brief outline of the technic followed at the Sea View Hospital: The blood is collected by a closed method using 100 cc. of a 2.5 per cent sodium citrate solution in distilled water for every 500 cc. of blood taken. During the collection the bottle is gently shaken to insure thorough mixing, and the bottle is then sealed and placed in the refrigerator, which is kept at 4° C. The blood is not disturbed until the transfusion is to be given. Before it is injected the blood is filtered through gauze and allowed to come to approximately room temperature.

Results.—In Table I are summarized the results of the transfusions of preserved blood in our series of twenty-eight cases. The cases are arranged according to the period of storage, those patients receiving fresh blood being listed first.

TABLE 1

RESULTS OF TRANSFUSIONS OF PRESERVED BLOOD IN A SERIES OF 28 PATIENTS

Age of patient, yrs.	Group and type — Patient	Group and type — Donor	Antisera used for distinguishing the transfused blood cells	Period of storage of donor's blood	Amount of blood transfused, c.c.	Reaction	1 day	2 days	1 wk.	2 wks.	3 wks.	4 wks.	5 wks.	6 wks.	7 wks.	8 wks.	9 wks.	10 wks.	11 wks.	12 wks.	13 wks.	14 wks.	15 wks.	16 wks.	17 wks.	18 wks.	19 wks.	End-point.	Remarks (P. T. = post-transfusion).
28	OM	ON	anti-M	3 hours	400	None	100	—	100	66	50	—	50	—	33	—	—	—	—	—	—	—	—	—	—	—	—	13 weeks	—
29	OMN	ON	anti-N	3 days	500	None	100	—	100	—	50	66	100	—	50	—	33	—	17	17	—	—	0	—	—	—	—	15 weeks	—
26	BM	BMN	anti-N	4 days	500	None	—	100	100	100	33	50	100	50	50	66	—	30	22	22	—	—	7	—	—	—	—	14 weeks	—
35	OMN	OM	anti-N	4 days	500	None	—	100	50	100	—	100	100	50	50	50	50	20	20	15	10	13	—	—	—	—	—	13 weeks	—
35	OMN	OM	anti-M	4 days	500	Chill	—	—	100	—	100	100	50	50	50	50	17	—	33	29	—	—	—	—	—	—	—	11 weeks	Transfusion stopped because of reaction.
23	BM	BMN	anti-N	4 days	350	T.→101° F.	—	—	—	100	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9 weeks	Patient developed septic temperature 7 weeks after transfusion.
26	OMN	OM	anti-N	4 days	500	None	100	50	66	66	100	100	50	66	50	66	20	33	33	20	10	7	—	—	—	—	—	10 weeks	Post-transfusion serum of patient slightly icteric.
6	DM	NMN	anti-N	5 days	300	None	50	50	50	50	—	—	—	—	—	—	—	—	50	13	29	—	—	20	10	—	—	13 weeks	—
26	OM	OMN	anti-N	6 days	500	None	100	100	100	33	33	33	—	33	—	13	0	—	—	—	—	7	—	—	—	—	—	16 weeks	Serum slightly icteric (P. T.).
11	BM	BMN	anti-N	8 days	500	None	—	—	66	100	100	66	66	50	50	7	7	0	—	—	—	—	—	—	—	—	—	7 weeks	Serum slightly icteric 21 hrs. later (P. T.).
50	AMN	AN	anti-M	8 days	500	None	—	—	50	—	—	0	25	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2 weeks	Serum slightly icteric 21 hrs. later (P. T.).
12	ON	OMN	anti-M	8 days	500	Chill T.→101.8° F	—	—	—	—	—	—	Patient was given several additional transfusions.															7 weeks	—
13	ON	OMN	anti-M	8 days	500	Chill T.→102° F.	—	—	—	—	0	33	33	33	13	—	—	—	—	—	—	—	—	—	—	—	—	7 weeks	—
14	ON	OMN	anti-M	8 days	500	Chill T.→101.6° F	33	—	—	66	65	0	—	20	13	10	7	0	—	—	—	—	—	—	—	—	—	—	—
15	AM	AN	anti-M / anti-N	9 days	500	(Postoperative) T.→103° F.	100	—	66	33	66	66	—	33	—	—	7	—	—	—	—	—	—	—	—	—	—	7 weeks	Serum slightly icteric 21 hrs. P. T.
16	AM	AMN	anti-N	11 days	500	T.→100.4° F.	—	100	66	66	—	66	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	9 weeks	Increasing icterus of serum until 21 hrs P. T.

																									Time	Remarks
17	21	AMN	anti-M	12 days	500	None (Post-op).	66			66	7	0	0					22								1 week	Icterus and hemoglobinemia.
18	20	BMN	anti-M	13 days	500	Chill T → 101° F.		20	22	25	16	23		13	0	22		20			50	65	100	66	50	2 weeks	Serum icteric 3 hrs. P.T.
19	21	AMN	anti-M	13 days	500	Chill T → 102° F.	50	50	15	25			50		20					13			100	66		5 weeks	Serum icteric 3 hrs. P.T.
20	31	OM	anti-N	14 days	500	Chill T → 101.8° F.				0	7	13					50	100	100				50		2 weeks	Serum icteric P.T.
21	29	OMN	anti-M	16 days	500	Chill T → 100.8° F.	33	33		15	15	22									33	66				---	Moderate icterus of serum 21 hrs. P.T.
22	23	BN	anti-M	17 days	500	Chill T → 101° F.	66	17	66	17	22	10		0					Patient left hospital.								—
23	38	AM	anti-M / anti-N	19 days	500	?	33	33		17	22		0				0		17			50	100				1 week	Icterus and hemoglobinemia.
24	31	AIBMN	anti-N	20 days	500	Chill T → 101.8° F. (Post-op).			33		17	0				17					33						3 weeks	Icterus and hemoglobinemia.
25	39	AIBM	anti-N	20 days	400	Chill T → 102.8° F.	13			0							10		0		50	33	100			1 week	Icterus of serum P.T., hemoglobinemia.
26	43	AMN	anti-M	21 days	500	Chill T → 102° F.	66	0	0												33	23	50	66		1 day	Icterus.
27	20	BM / ON / ON	anti-M / anti-(N) / anti-(N) / anti-B / anti-A	8 days / 2 days / 7 days	450 / 500 / 625	None (Post-op). / None / None		100	65	66		160	2nd Transfusion.	160	100	100	66	100	100	66	50	66		100	13 weeks (?)	Hemoglobinemia, hemoglobinuria, icterus.
28	39	OMN / AM	(anti-A) / anti-B / (anti-M) / (anti-N)	5 days / 3 days	400 / 500	None / None	100	200	100	100	100		100		66	50	100	50	0	0	7	7	15		15 weeks / 17 weeks / ? / 17 weeks	

711

To illustrate the interpretation of the results given in the table we shall describe the first case in detail:

This patient, twenty-eight years of age, belonging to group O (type M), was given a transfusion of 400 cc. of group O (type N) blood that had been drawn from the donor three hours previously. In this case the transfused cells could be followed with the aid of both anti-M and anti-N serum. In tests with anti-M serum, the agglutinated cells were the patient's, the un-agglutinated cells the donor's; in tests with the anti-N serum, the situation was reversed. The ratio of donor's to patient's cells gradually decreased following the transfusion so that, for example, five weeks after the transfusion only about half of the blood remained; seven weeks after the transfusion about one-third of the blood remained; and in tests made fifteen weeks after the transfusion, none of the donor's cells were demonstrable in the patient's blood. The end-point was taken as the time at which a small but definitely demonstrable amount of foreign blood was still present, in this case about thirteen weeks, when approximately one tenth of the donor's cells were still detectable.

From Table 1 it is evident that there is a negative correlation between the end-points and the periods of storage of the blood. This is shown rather strikingly in Fig. 94 where the end-points have been plotted graphically. The figure does not include cases 4, 7 and 21 since these patients left the hospital before all the transfused blood had been eliminated from their circulation, and case 14 is not included because this particular patient was given interfering additional transfusions before the end-point was reached. However, even in these four cases the data obtained are sufficient to indicate that the same general rule holds, namely, the survival time of the transfused cells in the patient's circulation is inversely proportional to the time that the blood was stored before the transfusions.

If we take the end-point for transfusions of fresh blood to be approximately 120 days, then the average decrease in the survival time was about six days for each day of storage, in the present study. It should be mentioned that there were variations, within limits, in the end-points of transfusions of blood stored for equal periods of time. As an extreme example, the five patients receiving eight-day-old blood can be cited; in these, the transfused erythrocytes were detectable for periods ranging from two to sixteen weeks. This lack of uniformity in the results among different patients can probably be traced in part to differences among different operators
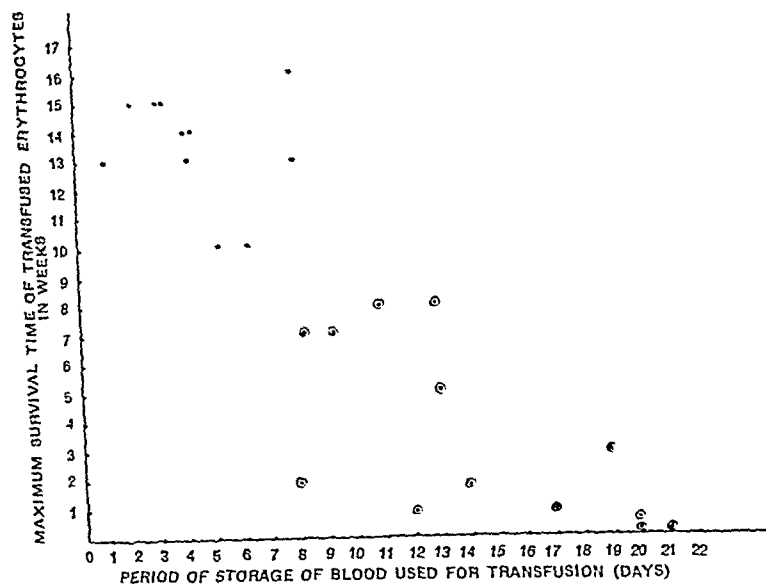
Fig. 94.—Scattergram of results of transfusions of preserved blood in 24 patients. Circle around dot indicates that serum of patients after transfusion was icteric.
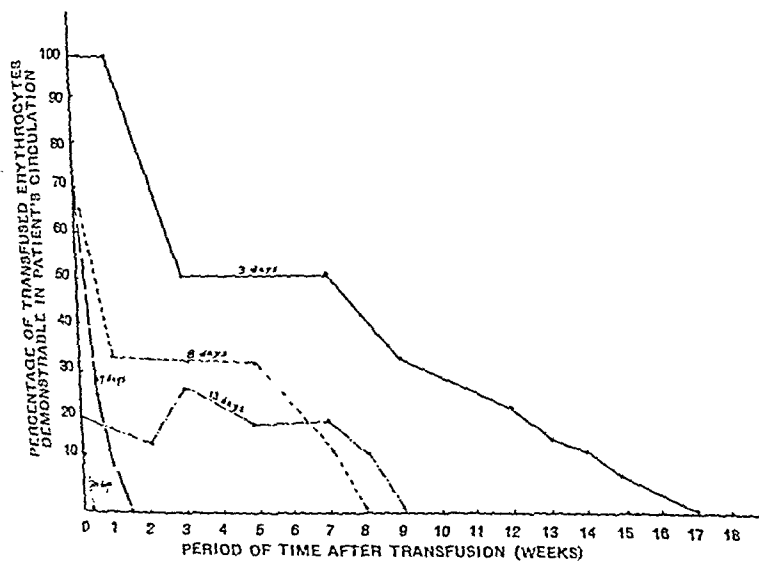
Fig. 95.—Percentage of translated blood cells surviving at varying periods following transfusion. (Five illustrative cases. Period of storage in days of blood used for transfusion is indicated on each curve.)

in the technic of collecting and handling the blood, and in part to the varying reactions of individual recipients to the blood which they received. At any rate, despite the fluctuations in the results of the individual blood transfusions, the influence of the period of storage of the blood on the survival time of the transfused erythrocytes in the patient's circulation is quite evident from inspection of either Table 1 or Fig. 94.

The results of each blood transfusion can also be demonstrated by plotting the percentage of transfused cells surviving at different intervals following the transfusion. A few illustrative curves are given in Fig. 95. If we consider that the efficacy of a transfusion depends on the number of functioning erythrocytes that it provides and the duration of life of these cells, the area under each curve would be a measure of the "usefulness" of the transfusion in question, and the end-point just discussed would merely be roughly proportional to the square root of the "usefulness." For example, on this basis, a transfusion with an end-point of eight weeks would be about ¼ as beneficial as one with an end-point of sixteen weeks, and a transfusion with an end-point of two weeks would be only ¹⁄₆₄ as beneficial. Accordingly, blood stored for periods longer than seven to ten days would be relatively inefficacious, as a rule, in comparison with fresh blood, for the treatment of anemias.

In the two cases receiving blood twenty and twenty-one days old, the donors' erythrocytes were eliminated from the circulations of the patients very rapidly. The transfusion of twenty-one-day-old blood was studied more closely than the others, and a number of samples of blood were drawn at short intervals from the patient during the first day following the transfusion. On all these specimens tests were made to determine the number of transfused erythrocytes remaining, and in addition the sera were separated and examined with the naked eye for the presence of hemoglobin or bile. In Table 2 are given the percentages of transfused blood cells detectable in the patient's circulation at varying times following the transfusion up to twenty-six hours. Despite the fact that ten minutes after the transfusion, all the donor's cells seemed to be intact, they evidently were fragile, as evidenced by their com-

TABLE 2

TRANSFUSION OF BLOOD PRESERVED IN VITRO FOR 21 DAYS (CASE 26, TABLE 1)

Time after completion of the transfusion.............	10 mins.	1 hr.	2 hrs.	3 hrs.	3½ hrs.	10 hrs.	24 hrs.	26 hrs.
Percentage of transfused erythrocytes surviving.........	100	66	66	66	66	10	5	0

plete breakdown within twenty-four hours of their injection and the appearance of hemoglobinemia and hemoglobinuria. In this case, therefore, the transfusion was practically of no benefit from the standpoint of supplying functioning erythrocytes; instead, the patient was subjected to the hazard of the possible development of a hemoglobin nephrosis.

As is shown in Table 1, there was only one chill among the patients receiving blood less than eight days old, while *reactions* occurred almost regularly among the patients receiving older blood. This reason has been given by workers[10] at the Cook County Hospital for setting their time limit for the storage of blood for transfusion at ten days. It should be pointed out, however, that while chills are to be avoided, if possible, since they are unpleasant to the patient, and in persons with cardiac disease may cause serious harmful effects, they are not a reliable criterion of the effectiveness of a transfusion. For example, transfusions also of fresh blood may be followed by chills, and yet the transfused erythrocytes survive the usual length of time (up to sixteen weeks). Indeed, until the importance of using solutions free of pyrogenic material was recognized, chills were accepted as a matter of course after any intravenous infusion. On the other hand, as in the case now to be described. it sometimes happens that blood of an incompatible group is unintentionally transfused without the occurrence of any detectable untoward reaction, despite hemolysis of the transfused cells:

The patient was a white woman, forty-nine years of age. who had had a hemorrhage following a tonsillectomy. The hemoglobin was 40 per cent, and blood study showed that the patient had myeloid leukemia. The patient's blood was typed as group B, and her blood was found to be compatible with the bloods of several group B professional donors. Nor was any sign of incompatibility detected by tests made in the cold by the centrifuge technic.[11]

The patient was then given three transfusions within twenty-four hours of 500 cc. each, from three of the compatible group B donors. There was no reaction of any sort following the transfusions, and the patient stated that she felt much stronger. Examination of the patient's blood two days later showed that the hemoglobin had risen to 67 per cent, but when retests were made four days later the hemoglobin was only 45 per cent. The drop in hemoglobin was attributed to the underlying disease. Twelve days after the transfusions the hemoglobin was still 45 per cent, and it was decided to give the patient another transfusion. It was now found that the patient's serum strongly agglutinated bloods of group B and at this time one of us (W.) was called into consultation. Reexamination of the patient's blood proved that she actually belonged to group O, not group B. At the same time, no trace of the group B cells injected twelve days previously could be detected in the patient's blood. A transfusion of 500 cc. of group O blood was then given, without untoward results.

The sequence of events in this case can be explained as follows: The patient belonged to group O, but for some reason—perhaps the underlying disease was a factor—her blood cells had a tendency toward nonspecific agglutination, so that two different individuals, using different testing sera, both grouped the cells as B. Originally, moreover, the patient's serum contained only α (or anti-A) agglutinins and lacked or contained only little β (anti-B) agglutinins. This explains why the mistake in grouping was not detected in tests of the patient's serum against standard cells, as well as the negative results of the cross-matching tests with group B blood. It also explained why the transfusions of a total of 1500 cc. of group B blood seemed to benefit rather than harm the patient. In the course of a few days, however, the patient's body began to react to the foreign B blood by producing immune anti-B isoagglutinins and gradually hemolyzing and eliminating the transfused erythrocytes (cf. Wiener[12]). This, rather than the leukemia, was responsible for the drop in hemoglobin and, as already mentioned, twelve days after the transfusions no trace of the injected B blood remained while compatible blood usually survives for periods up to 120 days. In this case, accordingly, though there were no untoward symptoms following the transfusion, the benefit derived was minimal, since the transfused erythrocytes survived and functioned for only a few days.

The case just described indicates that the survival time of the transfused erythrocytes is a more reliable criterion of the effectiveness of a transfusion than such clinical data as chills, fever and the subjective symptoms of the patient. One symptom that is of significance, however, is *jaundice,* since its appearance shortly after a transfusion implies that there has been partial or complete hemolysis of the transfused cells. Slight degrees of icterus, however, are difficult to detect merely by inspection of the skin or mucous membranes; a more sensitive and reliable method is to examine the patient's blood serum

for the presence of hemoglobin or bile. This procedure was followed as a routine in the present study, the serum being separated from a blood sample taken some time during the first day following the transfusion. As is shown in Fig. 94 and Table 1, none of the patients receiving blood stored for seven days or less developed icterus, two of four patients transfused with eight-day-old blood had icterus, while the sera of patients receiving older blood were icteric regularly. The icterus was usually only of short duration, and in most cases its presence would not have been noticed had the blood sera not been examined. Finally, as already mentioned, in patients receiving the blood stored for the longest periods, there was hemoglobinemia and hemoglobinuria as well as icterus. Our findings just described agree with those of Rosenthal[13] who remarks: "It seems that jaundice occurs infrequently after using blood less than a week old. It has been encountered after using blood beyond this period."

Discussion.—The limitations of transfusions of preserved blood compared to fresh blood transfusions are best presented by considering the various indications for the procedure. In brief, blood transfusions are given to raise the *blood pressure* by increasing the blood volume, to provide *functioning erythrocytes,* and to increase the *coagulability* of the blood. Transfusions are also given in infections to transfer natural or acquired *immune bodies* from donor to patient. The following discussion will be complicated somewhat since, often, transfusions are given to produce more than one of the effects just enumerated, *e.g.,* in sepsis, transfusions may be given to treat an accompanying anemia as well as the infection.

Where the need is primarily for *erythrocytes,* blood stored only a few days is almost equivalent to fresh blood. On the other hand, as already mentioned, our results indicate that blood stored longer than a week is relatively inefficacious. Similar conclusions have been reached by Kolmer,[14] based on the behavior of preserved blood *in vitro.* This worker states that the erythrocytes of preserved citrated blood showed evidences of swelling and dehemoglobinization as early as forty-eight hours after collection, degeneration progressing from day to day so that after fourteen days, as many as 30 per cent of the

cells were shadows, swollen and fragile (cf. Bagdassarov[15]). Kolmer believes that blood to be used for treatment of *anemias* should be stored no longer than two or three days.

On the other hand, in conditions where the prime purpose of a transfusion is to increase the *coagulability* of the blood, as in *hemophilia* and *purpura*,* fresh blood should always be used. Kolmer has demonstrated that in preserved citrated blood kept at 4° to 6° C.; the platelets show distinct clumping immediately, evidences of deterioration set in within twenty-four hours, the platelets becoming scarce at the end of forty-eight hours. According to Rhoads and Panzer[18] the prothrombin time of blood is greatly prolonged after only twenty-four hours of storage. In hemorrhagic diseases, therefore, the blood given to the patient should preferably be less than twenty-four hours old.

For the treatment of *acute hemorrhage,* bank blood stored less than a week is probably as effective as fresh blood, and the former has the advantage of its greater availability. In this connection, it is of interest to discuss the relative merits of fresh or stored citrated blood and fresh unmodified blood for transfusion. The latter has the advantage that no foreign substance is added to the blood, but has the disadvantage that the blood must always be injected rapidly to avoid clotting. In citrate transfusions, on the other hand, the blood can be injected as slowly as desired, a distinct advantage, particularly in cardiac patients or elderly patients with weak myocardia. In severe hemorrhages, however, the blood can be injected as rapidly as desired, since the blood vessels are partially collapsed and the blood pressure is low; in fact, speed is desirable. In such cases, when fresh or preserved citrated blood is used, one must bear in mind that the citrate is potentially toxic. Under ordinary conditions, when the citrated blood is given by the drip method, the citrate ion is oxidized in the body as rapidly as it is introduced,[21] and no harm results.† In fact, very large doses of sodium citrate can be given without the

---

* As a preoperative or postoperative adjuvant for jaundiced patients, blood transfusion is being displaced by therapy with synthetic or natural vitamin K.[16, 17]

† Incidentally, the injection of sodium citrate renders the urine alkaline, which is an advantage, since should a hemolytic reaction occur the prognosis is better when the urine is alkaline.[19, 20]

least harm to the patient provided that the injection is made slowly.[22] Rapid injections of relatively small amounts of the salt, however, have caused cardiac standstill, respiratory paralysis and death in experimental animals.[21] Accordingly, in those occasional severe hemorrhages, where massive transfusions are required within a few minutes, as in obstetrical hemorrhages, the transfusion of fresh unmodified blood would be the method of choice, if compatible donors are immediately available.

As an emergency measure in hemorrhage and shock, the intravenous injection of *citrated plasma* or *serum* has been advocated by a number of workers. In hospitals with blood "banks," when the expiration time of the blood is reached, the supernatant plasma can be siphoned off, and this can then be stored indefinitely. Aside from its keeping qualities, the use of plasma or serum is said to obviate the need of grouping tests. In the opinion of the writers, however, there should be no great trouble in keeping the plasma classified according to group and using plasma only of the homologous group, and this would eliminate the danger entailed in the injection of foreign isoagglutinins.[23] In traumatic shock, where the need is mainly to increase the blood volume, or in nephrosis, where transfusions are given primarily to provide serum protein rather than for erythrocytes, serum may serve as well as whole blood. The indefinite keeping qualities of serum give it all the advantages of gum acacia without the attendant dangers.[24] According to Levinson et al.,[25] *while whole blood is the best restorative agent in acute hemorrhages,* unless the hemorrhage is very extensive the loss of erythrocytes is not of serious importance, and plasma, by restoring the blood volume, is an effective agent in preventing and combatting shock. In any event, it is useful for emergency treatment until whole blood becomes available for transfusion.

In *infections,* one might expect as good results from bank blood as from fresh blood, considering the stability of natural and immune antibodies when stored *in vitro.* Thus, for the prophylaxis of infectious diseases such as measles, stored convalescent serum seems to be as effective as fresh whole blood or serum. According to Kolmer,[14] however, the bactericidal action of blood for many bacteria diminishes rapidly during

storage *in vitro*, and he advises that in infections only fresh blood should be used.

. For the sake of completeness, it should be mentioned that when preserved blood or serum *is used, rigid precautions are necessary to insure *sterility.* Cultural studies have shown that a substantial percentage of the bloods drawn may be infected,[28] particularly when the open method of collection is used. Although the contaminating bacteria or fungi are not pathogenic as a rule, they may be responsible for severe chills and fever following the transfusion. Bacteria can also break down or damage the red cells before the usual expiration date and thus give rise to hemolytic reactions. To avoid this eventuality, Diggs and Keith[26] suggest that before any stored blood is injected, the bottle be gently mixed, then a small amount centrifuged in a test tube and the supernatant fluid inspected for evidence of hemolysis. Novak[27] has suggested the addition of bacteriostatic drugs at the time that the blood is drawn.

. The observations of Scudder *et al.*[28] are also of importance. These investigators have demonstrated that in stored blood, a marked shift of potassium ions from the red cells to the plasma quickly occurs, and for this reason they advise against the use of blood more than five days old. For patients with nephritis such blood may be particularly harmful as potassium is more toxic to such individuals. However, since the blood is usually given by the drip method, the slow rate of injection would probably eliminate this source of danger just as it does for the sodium citrate that is injected.

Summary and Conclusions.—With the aid of a serologic technic, the time of survival of transfused erythrocytes was compared in patients receiving fresh blood and in those receiving blood that had been stored for varying periods up to twenty-one days. While fresh blood or blood only a few days old survived for periods up to three or four months, blood stored for longer periods disappeared from the patient's circulation sooner, the blood stored for as long as twenty-one days surviving only about twenty-four hours. The appearance of icterus could not be detected in patients receiving blood less than eight days old, while icterus regularly occurred, at times together with hemoglobinemia and hemoglobinuria, in patients receiving older blood.

The advantages and limitations of preserved blood in general were discussed. Based on our own observations and those of other independent investigators which have been reviewed here, we feel that the time limit for the preservation of whole citrated blood should preferably be set at *seven days*, and certainly not be allowed to exceed *ten days*.

BIBLIOGRAPHY

1. Huck, J. G., and Bigelow, R. M.: Poikylocytosis in Otherwise Normal Blood. Bull. Johns Hopkins Hosp., 34: 390. 1923.

2. Wildegans, H.: Die Lebensdauer direkt transfundierter Erythrocyten. Arch. klin. Chir., 139: 135, 1926.

3. Todd, C., and White, R. G.: On the Fate of the Red Blood Corpuscles When Injected into the Circulation of an Animal of the Same Species; with a New Method for the Determination of the Total Volume of the Blood. Proc. Royal Soc., B, 84: 255, 1911.

4. Ashby, W.: Determination of Length of Life of Transfused Blood Corpuscles in Man. Jour. Exp. Med., 29: 267, 1919.

5. Wearn, J. T., Warren, S., and Ames, O.: Length of Life of Transfused Erythrocytes. Arch. Int. Med., 29: 527, 1922.

6. Landsteiner, K., Levine, P., and Janes, M. L.: On the Development of Isoagglutinins Following Transfusions. Proc. Soc. Exp. Biol. and Med., 25: 673, 1928.

7. Wiener, A. S.: Longevity of the Erythrocytes. Jour. Amer. Med. Assoc., 102: 1779, 1934.

8. Dekkers, H. J. N.: Fate of Transfused Red Blood Cells. Acta med. Scand., 99: 511, 1939.

9. Perry, M. C.: Preservation of Blood for Transfusion. Wisconsin Med. Jour., 25: 123, 1926.

10. Fantus, B., Sud. L., and Schirmer, E.: Reactions to Blood Transfusion; Attempt at Etiologic Classification; Therapy Based Thereon. Arch. Path., 26: 160, 1938.

11. Wiener, A. S., and Peters, H. R.: Hemolytic Reactions Following Transfusions of Blood of the Homologous Group, in Press.

12. Wiener, A. S.: Blood Groups and Blood Transfusion, p. 98, 2nd Ed. C. C. Thomas, Springfield, Illinois, 1939.

13. Rosenthal, N.: Report of the Blood Bank of the Mount Sinai Hospital, Dec. 7, 1938.

14. Kolmer, J. A.: Preserved Citrated Blood "Banks" in Relation to Transfusion in the Treatment of Disease With Special Reference to the Immunologic Aspects. Amer. Jour. Med. Sci., 197: 442, 1939.

15. Bagdassarov, A.: Le problème de la transfusion du sang conservé. Le Sang, 11: 466, 1937.

16. Quick, A. J.: The Nature of Bleeding in Jaundice. Jour. Amer. Med. Assoc., 109: 66, 1937.

17. Doisy, E. A., Binkley, S. B., Thayer, S. A., and McKee, R. W.: Vitamin K. Science, 91: 58, 1940.

18. Rhoads, J. E., and Panzer, T. M.: Prothrombin Time of "Bank Blood." Jour. Amer. Med. Assoc., **112**: 309, 1939.

19. Baker, S. L., and Dodds, E. C.: Obstruction of Renal Tubules During Excretion of Hemoglobin. Brit. Jour. Exp. Path., **6**: 247, 1925.

20. DeGowin, E. L., Ostenhagen, H. F., and Andersch, M.: Renal Insufficiency from Blood Transfusion; Relation to Urinary Acidity. Arch. Int. Med., **59**: 432, 1937.

21. Salant, W., and Wise, L. E.: Action of Sodium Citrate. Jour. Biol. Chem., **28**: 27, 1916.

22. Marriott, H. L., and Kekwick, A.: Continuous Drip Blood Transfusion, with Case Records of Very Large Transfusions. Lancet, **1**: 977, 1935.

23. DeGowin, E. L.: Hemolytic Transfusion Reaction Produced by Blood of "Universal Donor." Jour. Amer. Med. Assoc., **108**: 296, 1937.

24. Studdiford, W. E.: Severe and Fatal Reactions Following the Intravenous Use of Gum Acacia Glucose Infusions. Surg., Gynec. and Obstet., **64**: 772, 1937.

25. Levinson, S. O., Neuwelt, F. and Necheles, H.: Human Serum as a Blood Substitute. Jour. Amer. Med. Assoc., **114**: 455, 1940.

26. Diggs, L. W., and Keith, A. J.: Problems in Blood Banking. Amer. Jour. Clin. Path., **9**: 591, 1939.

27. Nowak, M.: Preservation of Stored Blood with Sulfanilamide. Jour. Amer. Med. Assoc., **113**: 2227 (Dec. 16) 1939.

28. Scudder, R. J., Drew, C. R., Corcoran, D. R., and Bull, D. C.: Studies in Blood Preservation. Jour. Amer. Med. Assoc., **112**: 2263 (June 3) 1939.

CONTRIBUTION BY DR. HENRY A. BARRETT

NEW YORK CITY

THE IRRADIATION OF AUTOTRANSFUSED BLOOD BY ULTRAVIOLET SPECTRAL ENERGY: RESULTS OF THERAPY IN 110 CASES

SINCE Niels Ryberg Finsen (1860–1904), by general consent the father of scientific ultraviolet radiation therapy, brought the healing action of this form of radiant energy to the attention of the medical world, as a result of his treatment of lupus vulgaris, many members of the profession as well as other scientists have sought to determine the physiologic effects of ultraviolet spectral energy and its therapeutic efficacy in many other conditions.

There exists, as a result of their labors, an extensive literature dealing with all phases of the subject. Those physicians who have been guided by the precepts of such authorities as Rollier. Gauvain, Bernhard, Hill, Stewart Duke-Elder, and others have obtained results with ultraviolet that have been gratifying to themselves and to their patients. They have come to respect this form of radiant energy for what it is—a most valuable gift to mankind for the prevention and alleviation of numerous ills and the maintenance of sound health.

It would scarcely seem necessary to stress the importance of a thorough grounding in the physics, biophysics and technical therapeutic procedures of ultraviolet radiation were it not for the fact that there exists in the profession today a skepticism about this agent and even antagonism to it which may be traced directly to a disregard for authoritative guidance on the part of many users of this form of spectral energy.

In the light of our present knowledge of ultraviolet spectral energy the following statements will serve as a partial explanation of its remedial action as well as its occasional deleterious effects:

PHYSIOLOGIC ACTION AND EFFECTS OF ULTRAVIOLET ENERGY

1. Ultraviolet rays, as such or by virtue of their activating powers on animal and plant substances, exert a profound influence on calcium metabolism. Consider rickets, osteomalacia and spasmophilia. The exact modus operandi is unknown.
2. Bacteria in the body are killed by direct action, and indirectly by increasing local and systemic resistance.
3. Toxins in and out of the body are rendered inert.
4. Ultraviolet rays tend to restore normal chemical balances in the body.
5. In suitable doses it tends to correct cellular imbalance in the blood.
6. Lipoidal elements in the blood (chylomicrons) which are altered in character by disease are restored to normal size and Brownian movement by ultraviolet, both *in vivo* and *in vitro*.
7. There is an increase in oxygen absorption values in the blood following ultraviolet irradiation (hemo-irradiation) of autotransfused blood.
8. Ultraviolet radiation has a cumulative effect.
9. Individuals vary greatly in their sensitiveness to ultraviolet irradiation as regards skin reactions and systemic effects. The same individual will vary in different states of health. Sensitiveness may be modified by certain drugs (sulfanilamide), foods (buck-wheat), and pathologic substances (hematoporphyrin).
10. Overdosage produces depression, lessened resistance to bacterial infection and reduced bactericidal potency of the blood, and a fall in red cells and hemoglobin.
11. The action of ultraviolet rays may be immediate, somewhat delayed, markedly delayed, or protracted. The action may also be classified as "primary" and "secondary."

This partial list indicates but does not completely explain the complicated physiologic action and effects of ultraviolet radiation. For a more detailed outline the reader is referred to an article by Henry Laurens in the Journal of the American Medical Association, December 24, 1938.

It is apparent that, in administering this agent, which is capable of *doing harm as well as good,* many factors must be borne in mind in order to select cases suitable for therapy and also for proper selection of dosage.

Conventional ultraviolet therapy consists in the exposure of the skin, mucous membranes, and other tissue surfaces to some source of ultraviolet spectral energy, either the sun or an artificial source, whereas in *hemo-irradiation,* citrated blood is exposed to these rays.

Some conception of the powerful *chemical action* of ultra-

violet radiation may be formed by a consideration of the work of W. T. Bobie, a biophysicist, with paramecia. He was able to kill these animacules in a fraction of a second with a comparatively weak source. Coblentz, of the Bureau of Standards, killed bacteria in a fraction of a second under certain experimental conditions. The water-cooled mercury quartz lamp used in our work produces on the skin of the forearm, inner side, an erythema after one to two seconds' exposure and a desquamation with two to three seconds exposure, at contact.

In blood, we have a medium in which float delicate cells not unlike in essential chemical respects paramecia and bacteria. Many of the blood cells in the superficial strata in the irradiation chamber we are using are in a highly exposed state and receive the full force of the intense ultraviolet bombardment from the lamp used at contact, the actual source or burner being only about an inch away. In the light of the experimental work with paramecia and bacteria just mentioned, it is easy to predict what the fate would be of many blood cells which pass through the irradiation chamber if these were subjected to prolonged exposure. Other blood cells and blood elements are affected in varying degree, depending upon the amount of irradiation received in accordance with von Grotthus' law governing absorbed radiant energy and chemical effect.

By employing the Knott technic of hemo-irradiation which is about to be described, there appears to be an absence of any harmful effect on blood cells and elements as well as almost no occurrence of transfusion reactions. At least no harmful effects have been detected thus far.

My interest in ultraviolet hemo-irradiation was reawakened by a chance meeting with an old acquaintance, Mr. E. K. Knott of Seattle, while he was visiting New York in 1936. He told me of some experimental work with ultraviolet rays he and a medical student, now Dr. Edblom of Eugene, Oregon, had conducted in 1926, 1927, and 1928 on the blood of dogs. After a great deal of investigation they evolved a technic of ultraviolet hemo-irradiation that invariably sterilized the blood of these animals after an artificial septicemia had been produced. The organisms used were *Streptococcus haemolyticus* and *Streptococcus albus* and *aureus*. At the height of the

septicemia, the dogs were given irradiations, following which blood cultures were made. Even though these were invariably returned negative within twenty-four to seventy-two hours, the dogs without exception died about the seventh or eighth day from what closely resembled anaphylactic shock. It was finally discovered that deaths were due to over-irradiation. By continued experimentation Knott and Edblom were eventually able to discover the safe volume limits of blood to irradiate, as well as proper time factors and the optimum intensity, which enabled them to clear up the blood stream infection without fatalities to the animals.

In 1928 Knott irradiated the blood of his first human subject. It was a case of sepsis and blood stream infection following abortion. The patient, who was declared beyond help by the attending physicians, responded favorably to the irradiation, lived, has since borne a child, and is alive today. The method soon came to the attention of Dr. Virgil K. Hancock of Seattle and the late Dr. Tate Mason. In the Virginia Mason Hospital of Seattle, the majority of the subsequent hemo-irradiations have been made.

As one who had nearly twenty years experience with ultra-violet radiation, I was happy to hear about a new technic which seemed to eliminate some of the ungovernable factors present in the conventional methods. Mr. Knott explained the details of his method, which I have since carefully observed in my work. With the exception of the Knott method I am unaware of any way of irradiating the blood by means of ultra-violet spectral energy and returning this blood to the circulation with benefit to animals or human beings. However, I do know of several unsuccessful attempts that have been made with the use of other technic.

I am convinced as a result of my own experience and the work of others with which I am familiar, that certain details must be observed to achieve satisfactory results even with this method. Only by using the technic advised by Knott, and by employing the Knott irradiation chamber with a relatively low time factor, can *consistently successful* results be obtained in this field of therapy.

The Knott Technic of Hemo-irradiation.—The *irradiation chamber* is of circular shape, 2 inches in diameter, and

approximately 1 inch deep. Two outlets extend from the sides to which transfusion tubing may be attached. Connecting the outlets within the chamber is a labyrinthed channel faced with a quartz window against which the water-cooled mercury quartz lamp is held.

Early workers exposed blood to ultraviolet radiation for from minutes to hours and even recent experimenters have used long time factors. Frequently in the past the intensity of the source was rarely determined and was often inconstant. With the Knott method the *time of exposure*, the *quality* and *intensity of the radiation*, as well as the *penetrability*, are fairly constant.

A predetermined amount of blood is withdrawn, based on the *age, size*, and *general condition* of the patient and the *nature* of his disease. The smallest amount of blood irradiated in my series was 75 cc., the largest amount 400 cc. After withdrawal the blood is *citrated* with a 2.5 per cent solution of sodium citrate and returned immediately to the circulation by gravity. The *rate of flow* is controlled by digital pressure on the tubing at the outlet of the chamber. The *voltage* across the burner of the lamp was in nearly all cases 50 volts, but in a few, 65 volts. The *time* of irradiation was ten to thirty seconds, depending on various factors. This is, in a wide range of conditions, the technic employed by those authorized to use this method.

Results of Hemo-irradiation.—The 110 patients whose cases I am reporting have received a total of 208 irradiations. varying from a single treatment in some cases to eight in one case. Some of the outstanding results have been obtained with a *single* irradiation. Some individuals have not noticed any improvement with a single treatment but have with the second or third. I feel sure that my statistics would be better than they are had several persons had more than a single treatment and not become discouraged by failure to respond to the first and only one taken.

Patients with varied pathologic conditions were irradiated (Table 1), and the work was not confined to one or two diseases because I felt certain that no harmful effects would be produced after some preliminary trials and I was anxious to find out how many different conditions could be influenced by

TABLE 1

Various Conditions Treated by Hemo-irradiation with Ultraviolet Rays
(110 Cases)

Condition.	Cases.	Symp-tom-free.	Marked improve-ment.	Moder-ate improve-ment.	Slight improve-ment.	Fail-ures.	No con-tact.	Died.	Average number of treat-ments.
Asthma.........	7	1	5	..	..	1	..	..	1.5
Arthritis, infectious (rheumatoid)........	13	6	1	2	1	2	1	1	2.0
Arthritis (osteo)......	16	1	5	2	2	6	4	.	2.0
Debility........... .	34	16	11	5	..	2	.	.	1.5
Tbc. glands...........	2	..	2	.	.	.	.	..	2.0
Tbc. eye.............	1	..	..	1	..	..	..	..	5.0
Blepharitis, chronic....	4	.	2	1	1	..	..	..	2.5
Keratitis, chronic recurrent...............	1	1	..	..	..	..	..	..	4.0
Postpartum sepsis.....	1	..	..	..	..	1		1	1.0
Mastoiditis.......... .	1	1	.	..	..	.	.	..	1.0
Dermatitis............	2	..	1	.	.	1	..	.	4.5
Pruritus ani..........	2	..	..	.	.	2	.	..	1.0
Colds, severe recurr...	1	..	1		..	..	.	.	2.0
Uveitis	1	.	1	.	..	..		..	2.0
Furunculosis..........	2	1	1	.	.	.		..	2.5
Bronchitis, severe acute.	1	1		.		..	..		2.0
Sinusitis, chr. paranasal.	4	.	1	2	..	1			2.0
Blood stream infection (Str. vir.)...........	2	..	.			2		2	1.0
Blood stream (pneu-mococ.).............	2	..	.	.	..	2	.	2	1.0
Acne vulgaris........	3	1	2			.			3.0
Sciatica.............	1			.		1		.	2.0
Allergy (food)......	1	.	1						2.0
Epilepsy............	3		1			2			2.0
Anemias, secondary....	8	5	1	1	..	1	.		2.0
Filariasis............	1	.				1	1		1.0
Leukemia, acute spleno-myelog.	1	.				1	.		1.0
Marie Strumpel's D. .	1	..	1				.		3.0
Combined sclerosis....	1					1		.	1.0
Lateral sinus throm-bosis..............	1		.	..		1		1	1.0

There are twenty-nine different conditions listed above in these 110 pa-
tients. Cases listed as "no contact" are set down as failures. A sense of

this method. A trial of the method in *eye conditions* was suggested by Duke-Elder's article in the British Journal of Ophthalmology in June, 1928, entitled "Ultraviolet Light in the Treatment of Ophthalmic Diseases." Some of my friends in this specialty supplied me with a number of cases, and this part of the investigation is continuing under their guidance and will be reported in a few months. Most of the cases of all kinds have come from medical friends who have been encouraged to assist in the irradiations and to follow their results. Cases have not been selected with the thought of statistics in mind. For the most part the cases have been stubborn ones that refused to respond to other forms of therapy after a fair trial. Unless it were imperative that other medication be continued, as in some cases with cardiac involvement, all medication was stopped in accordance with good experimental practice.

In conventional ultraviolet therapy, one does not expect to observe any appreciable change in a patient's condition under twenty-four hours at least, and seldom under several days. With hemo-irradiation, however, I have seen patients suffering from *infectious* or *rheumatoid arthritis* improve remarkably within a few hours. A few days ago I treated a sufferer from this disease who received complete relief from pain the next morning. Another patient with a similar condition who came to me, not because of her arthritis but because of severe night sweats necessitating a change of linen three and four times a

---

increased well-being which lasted for a few days only was not considered to have been a sufficient response to treatment. The patients with pruritus ani and sciatica, for example, reported immediate relief which lasted only a few hours. The patient with mastoiditis had been ill for nineteen days. *x*-Rays showed a 4 plus mastoid with softening. She refused operation but consented to hemo-irradiation. She was back at work in six days symptom-free and has remained so for over a year. (It must not be inferred that I am advising this form of treatment for mastoiditis because of apparent success with one case. I do believe, however, that hemo-irradiation is a measure to be strongly recommended, both pre- and postoperatively, especially if infection is present.)

The greater number by far in the above series were old chronic cases which had received conventional medication and other forms of therapy. I had very few "easy" cases. Wherever possible other measures were stopped before the irradiation.

night, winter and summer, had her perspiring reduced to half the usual amount the night of the day of the irradiation, with complete relief of not only the sweating but also the arthritis after the third irradiation. She has been symptom-free over a year.

I have witnessed a patient with *chronic blepharitis,* treated by a specialist for two years by phages and bacterins and other medication and referred by him for hemo-irradiation because of failure to respond to treatment of any kind, cease to lacrimate the next day and such lacrimation has not started again after an interval of several months. Eczema of the lids was gone in less than a week and the severe conjunctivitis has almost completely disappeared.

Another case which illustrates the rapid response to hemo-irradiation frequently seen is the following one: In March of this year one of my associates in this investigation assisted me in the irradiation of a patient of his suffering from *bronchial asthma* of four years' duration. The patient, aged forty-five, had been in the hospital for several weeks and in spite of all medication was having several attacks daily. During the irradiation she had two attacks. Her doctor reported the next day that she had had only one attack in twenty hours. After that, she had an occasional attack, not more than two or three a week. The attacks became fewer and fewer and have been entirely absent for several months.

There are many cases which demonstrate the remarkable improvement in *toxemias* following irradiations. My experience in this regard parallels that of others using this method.

Mortality.—In my series there have been six deaths, and in fairness to the method these should be discussed:

Two patients with septicemia due to *Streptococcus viridans* were given a single irradiation at a hospital located some distance from New York. No equipment was available at this hospital save the transfusion apparatus and it necessitated transporting a heavy water-cooled lamp and other apparatus from my office. Whether satisfactory results would have been obtained by a series of irradiations is open to question, but only a single treatment was given. Death resulted in both cases several months afterwards.

Another case was that of a boy, aged nine, suffering from *lateral sinus thrombosis, double bronchopneumonia* and *septicemia*. It was my plan to give at least two irradiations, the first one being with small dosage because the patient had had sulfanilamide for several days and this is a sensitizing drug. The boy developed jaundice the next day and another irradiation was not permitted by the attending physicians. The boy succumbed five days after the single irradiation.

I was asked to treat a *diabetic* who developed *septicemia* after prostatectomy. He was given sulfanilamide for forty-eight hours and, when seen by me, was in coma. Cheyne-Stokes breathing was present and his blood sugar was 275 mg. The patient died during the night, six hours after the irradiation.

A case of *infectious arthritis* complicated by severe *cardiac involvement* with *decompensation* was treated by me over a year ago. The patient recovered completely from her arthritis, was symptom-free for several months, but died eventually from cardiac failure.

Another patient with *double pneumonia* and *septicemia* was irradiated in his home. Because of a variety of circumstances and difficulties encountered in performing the hemo-irradiation, the irradiation could be only incompletely done. The man lived forty-eight hours after the treatment, dying before it was feasible to give him another.

Summary and Conclusions.—From an experience with 110 patients so far treated (February 16, 1938, to October 15, 1939), it can therefore be truthfully asserted that:

1. No detrimental reactions from ultraviolet irradiation have been observed. With the factors employed it is a very safe method.
2. Improvement is frequently almost immediate.
3. The field of usefulness of ultraviolet therapy has been considerably widened by the Knott method.

Physiologic effects commonly observed may be summarized as follows. There is an:

1. Increase in peripheral circulation.
*2. Increase in the combining power of blood and oxygen

3. Inactivation of toxins in the blood.

4. Increased resistance to infection.

BIBLIOGRAPHY

* George P. Miley: Effect of Hemo-irradiation of the Oxygen Combining Power of the Blood. Proc. Philadelphia Physiological Society, April, 1939.

(Note: An original draft of this paper was read at the Broad Street Hospital, New York, Nov. 3, 1939.)

CLINIC OF DR. NORMAN JOLLIFFE

DEPARTMENT OF MEDICINE, NEW YORK UNIVERSITY COLLEGE OF MEDICINE, AND THE MEDICAL SERVICE OF THE PSYCHIATRIC DIVISION, BELLEVUE HOSPITAL

RECENT ADVANCES IN THE THERAPEUTIC USE OF THE B VITAMINS

THERE are now available in crystalline form for clinical use four of the B vitamins. These are *thiamin chloride, riboflavin, nicotinic acid,* and *vitamin B_6 hydrochloride.* By the use of these chemical substances the clinical investigator has been enabled to make several advances in the diagnosis and treatment of deficiency diseases. To illustrate these advances, the · following clinical record is presented:

Illustrative Case.—V. B., a thirty-four-year-old white female, was transferred to the Medical Service of the Psychiatric Division of Bellevue Hospital from an institution for the care of epileptics where she had been a patient for the past five years. When admitted she complained of weakness, bleeding gums, sore mouth and tongue, and a rash on the face and hands, all of some few weeks' duration. Her history included epileptic convulsions since the age of three. Her diet had consisted chiefly of the following: breakfast—oatmeal, coffee, white bread; lunch—white bread and butter, potatoes, a portion of stew; supper—tea, white bread and butter, prunes and apricots. She received one egg each week. The meat in the stew was never eaten by the patient but was given to others. In addition she consumed daily large amounts of cake furnished by her parents, so that the main constituents of her diet were cake and white bread.

Examination on admission showed a thin, undernourished, chronically ill female. She was cooperative and completely oriented. The epithelium of the lower lip showed degeneration, with scaling and desquamation (cheilosis). There were fissures at the angles of the mouth extending about 2 mm. laterally in each direction from the mucocutaneous junction. There was moderate maceration of the tissues in the angles of the mouth. In the nasolabial folds and across the bridge of the nose there was a seborrheic lesion consisting of filiform excrescences, about 0.5 mm. in length, which appeared to protrude from the sebaceous glands. Superficially this lesion resembled urea frost, but it could not be rubbed off and the underlying skin felt greasy. In addition to this

lesion there was an acneform eruption over the face. The upper jaw was den-
tureless. The gums of the lower jaw were red and markedly piled up, con-
sisting of bags of blood which bled on light touch. The tongue was clean,
bald, and reddened, as were the oral mucous membranes. Along the frenulum
of the tongue were ulcerations covered by a pearl-gray exudate. On the right
hand there was deep pigmentation over the second interphalangeal joint and
thumb, a small ulceration over the knuckles, and a bracelet-like pigmented
dermatitis of the wrist. The left hand exhibited a bracelet-like pigmented
dermatitis and slight dermatitis over the second interphalangeal joint. There
was no evidence of peripheral neuritis. A diagnosis of riboflavin, nicotinic acid
and cevitamic acid deficiency, and epilepsy, was made.

The patient was maintained with the diet poor in vitamin B complex.[1]
Studies of the blood revealed total absence of cevitamic acid. The patient
was then given 300 mg. of cevitamic acid daily by intravenous injection, and
100 mg. four times a day by mouth. On the second day of this regimen there
was definite improvement, and on the following day the gums were natural in
color. The stomatitis and glossitis had remained unchanged. The dosage of
cevitamic acid was then reduced to 200 mg. daily by mouth, while the diet
poor in vitamin B complex was continued. From the sixth day of hospitaliza-
tion the patient was given 500 mg. of nicotinic acid daily, in doses of 100 mg.
each, by mouth. By the eighth day of hospitalization the abnormal redness of
the tongue and mucous membranes of the mouth had disappeared, the frenulum
ulcer had healed, and the dermatitis of the hands was clearing. The lesions
on the face and lips, however, were unchanged.

Beginning on the seventeenth day of hospitalization, the administration of
nicotinic acid was discontinued, but the patient was still maintained with the
diet poor in vitamin B complex; in addition, 10 mg. of synthetic riboflavin
was administered daily by mouth. On the fifth day of this regimen a definite
and marked improvement was noted. The degenerative epithelial lesion of the
lips and the fissures at the angles of the mouth had cleared entirely, and the
filiform lesions on the nasolabial folds and bridge of the nose had disappeared;
the acneform rash had also improved. The patient, however, now showed
definite signs and symptoms of a mild peripheral neuritis characteristic of
vitamin B_1 deficiency. She was then given 50 mg. of thiamin chloride daily
by intramuscular injection. This was followed within three days by complete
disappearance of the signs and symptoms of peripheral neuritis. From this
time (the twenty-seventh day of hospitalization) the patient was given the
house diet supplemented daily by 200 cc. of orange juice and 18 gm. of vegex,
and the administration of riboflavin, cevitamic acid and thiamin chloride was
discontinued. The strength of the patient now markedly improved, and her
weight increased from 84 pounds, on the day this regimen was initiated, to
111 pounds, when she was discharged twenty-six days later.

The course of this patient illustrates two *diagnostic* and
two *therapeutic* points, each of which will be discussed:

1. *By the use of specific chemical substances the clinical
investigator has been enabled to differentiate to some extent
between the specific signs and symptoms of several deficiency*

states in man. The swollen, spongy bleeding gums responded promptly to cevitamic acid therapy, leaving all the other manifestations. In the present clinic we will not concern ourselves with scorbutic manifestations other than to point out that a patient having a stomatitis due to nicotinic acid deficiency may present simultaneously a scorbutic gingivitis.

Nicotinic Acid Deficiency.—The *signs* and *symptoms* of *nicotinic acid deficiency*, as manifested in this patient, were the scarlet red stomatitis, glossitis, ulcerations of the floor of the mouth, and the dermatitis of the hands.

All these manifestations were cured by nicotinic acid. This patient did not, however. present all the signs and symptoms of chronic nicotinic acid deficiency, which include not only the *oral lesions* and *bilateral dermatitis* but, in addition, *diarrhea, inflammation* of some or all *mucous membranes*, and *mental changes.* These lesions, in combination, form such a characteristic picture that they are widely recognized.

It is not so well understood, however, that the oral lesions, the gastro-intestinal lesions, the mental changes, or the skin lesions may each occur alone or in any possible combination. For example, patients having the stomatitis of nicotinic acid deficiency are too frequently considered to have only the superimposed Vincent's infection. The primary diagnosis is, consequently, not considered, and specific therapy is often neglected. If nicotinic acid therapy is instituted, not only will the scarlet red stomatitis blanch within from twenty-four to forty-eight hours, but the Vincent's infection usually heals without other general or local therapy. The mental changes may precede the skin, gastro-intestinal or oral changes and the patient may be labeled as a neuresthenic, neurotic, or psychoneurotic. These signs and symptoms have been pointed out by Spies, et al.[2]

In addition to the common mental symptoms there exists a well defined neurologic and mental syndrome which we[3] have labeled as *nicotinic acid deficiency encephalopathy.* This syndrome consists of progressive stupor, changing cogwheel rigidities of the extremities, and uncontrollable grasping and sucking reflexes. In about half the subjects this syndrome may be the only manifestation of nicotinic acid deficiency, but it may occur in the presence of other recognized signs of this defi-

ciency. It may also be associated with vitamin B_1, riboflavin, or vitamin C deficiency. Prior to our recognition of its etiology this syndrome was almost universally fatal. Since the use of nicotinic acid, the mortality has been reduced to approximately 15 per cent.

Riboflavin Deficiency.—The cheilosis, the angular oral fissures, and the filiform dermatitis of the face were the manifestations of *riboflavin deficiency* in our patient. This syndrome was first recognized as a riboflavin deficiency by Sebrell and Butler,[4] who produced it in a group of subjects maintained with a diet deficient in this vitamin. It is not rare in the northeastern United States. We[5] have recently reported from this service fifteen patients having this syndrome. Spies, Vilter and Ashe[6] have reported forty patients with similar lesions, mostly endemic pellagrins. Sydenstricker[7] finds it more common in Georgia than frank pellagra. This syndrome consists of facial lesions characterized by filiform excrescences of seborrheic nature, apparently deriving from the sebaceous glands; the lesions vary in length up to 1 mm., and are closely to sparsely scattered over the skin of the face. Their characteristic location is in the nasolabial folds, but in addition they occur frequently on the alae nasi, occasionally on the bridge of the nose, and sometimes on the forehead above the eyebrows. The skin on which these filiform excrescences are located is the seat of a fine, scaly, greasy desquamation. In addition to these facial lesions, most of the patients show fissuring and maceration at the angles of the mouth, and a degenerative crust-like formation on the epithelium of the lips, most marked on the lower. The fissures at the angles of the mouth are bilateral, and extend laterally 1 to 3 mm. onto the mucous membrane of the mouth and for 1 to 10 mm. onto the skin. They are usually very shallow, but they may be 0.5 mm. in depth and their base, as a rule, shows little or no increased redness. Extending for a distance of from 5 to 20 mm. from the angle of the mouth onto both the upper and lower lip, the mucous membrane is macerated and wrinkled and of a pearl-gray color. The lips, particularly the lower, frequently show a marked increase in the vertical fissuring, often without a break in the mucous membrane. Occasionally, the vestibule of the nose is involved with lesions similar to those on the lips.

Vitamin B$_1$ Deficiency.—The *polyneuritis*, developed while the patient was maintained with the diet poor in vitamin B complex, was a manifestation of *vitamin B$_1$ deficiency*, and it disappeared quickly when crystalline vitamin B$_1$ was administered. The signs and symptoms attributed to this deficiency are legion, the most definite being anorexia, fatigue, and a neurologic and a circulatory syndrome. Anorexia and fatigue are non-specific. In their presence the possibility of vitamin B$_1$ deficiency should be considered and confirmatory signs should be sought. When these symptoms do not respond definitely to thiamin therapy within seventy-two hours, they are probably not due to vitamin B$_1$ deficiency alone.

The *neurologic manifestations* are those of bilateral and symmetrical polyneuritis involving first and predominantly the lower extremities. We[8] have classified these neurologic manifestations according to severity into four groups: (1) *suggestive,* (2) *mild,* (3) *moderate,* and (4) *severe.* Heaviness of the lower extremities, and calf muscle cramps are usually the first symptoms. These are followed by paresthesias in the toes and fingers, burning of the feet, and pain in the legs. It should be emphasized that pain, though nearly always present, can often be elicited only by a leading question. Calf muscle tenderness and plantar hyperesthesia may extend up the ankles and legs in a sock distribution. Vibratory sensation may be lost in the toes. These signs we classify as *suggestive,* and a positive diagnosis of polyneuritis is not made, as circulatory disturbances may cause these or very similar findings. However, when in addition to these signs, the ankle jerks are absent, a diagnosis of *mild* polyneuritis can be made. As the deficiency continues, the sensory and motor changes advance, the knee jerks disappear, position sense in the toes becomes impaired, calf muscle atrophy develops, and foot drop follows. We classify this degree of involvement as *moderate,* provided the signs are confined to the lower extremities. When there is also involvement of the upper extremities, the spinal cord, or the cranial nerves, or when a "central neuritis" is present, we classify the polyneuritis as *severe.*

The *circulatory manifestations* of vitamin B$_1$ deficiency do not form a rigid clinical picture. They may occur in a person whose circulatory system is otherwise normal; or they may be

superimposed on one previously damaged by degenerative, hypertensive, or inflammatory disease. We[8] have classified the circulatory manifestations as follows: (a) Edema and serous effusions occurring in the absence of congestive heart failure, enlarged heart, and recognized etiologic factors producing edema and serous effusions. (b) Edema and serous effusions occurring with supporting signs and symptoms of congestive heart failure, usually with definite roentgenographic evidence of cardiac enlargement. (c) Sudden circulatory collapse which may be the first manifestation of circulatory failure or which may occur after other signs of circulatory failure are well advanced.

2. *By the use of specific chemical substances the clinical investigator has demonstrated that some deficiency syndromes heretofore believed to be etiologic entities represent multiple deficiencies.*

Two years ago our case would have been presented as one of pellagra complicated by scurvy. The cheilosis, angular oral fissures and filiform dermatitis, now recognized as manifestations of ariboflavinosis; the polyneuritis, now known to be a manifestation of thiamin chloride deficiency; and the stomatitis, glossitis, and dermatitis of the hands, now known to be due to nicotinic acid deficiency—would all have been correctly labeled under the single designation, pellagra. The patient would have been treated with a high caloric mixed diet supplemented with large amounts of brewers' yeast or vegex or aqueous liver extract. These various manifestations of pellagra would have responded promptly, but such therapy would never have demonstrated the *multiple* deficiency nature of pellagra.

That the *polyneuritis* occurring in *pellagrins* is a separate entity was first recognized after thiamin chloride became available. This was demonstrated by Spies and Aring[9] and by Jolliffe and Goodhart.[10] Following the use of nicotinic acid for pellagra, it was soon discovered that not all the remaining signs attributed to a deficiency of the P.–P. factor could be cured by this substance.[6] After the experimental production of the lesions of ariboflavinosis by Sebrell and Butler,[4] several investigators[5, 6, 7] almost simultaneously found that the similar lesions occurring in pellagrins were manifestations of riboflavin deficiency.

3. *By the use of specific chemical substances the clinical investigator has been enabled to demonstrate that signs and symptoms of a specific deficiency respond promptly to adequate amounts of a specific chemical substance if the pathologic changes are not so advanced as to be irreversible.*

The swollen, spongy, bleeding gums of our patient responded promptly to cevitamic acid; the stomatitis, glossitis, ulcerations of the floor of the mouth and dermatitis of the hands responded to nicotinic acid; the cheilosis, the angular oral fissures and the filiform dermatitis of the face responded to riboflavin; and the polyneuritis responded to thiamin chloride.

4. *By the use of these chemical substances the clinical investigator has learned that complete recovery of the patient does not always follow, and adequate treatment does not consist of the administration of these specific chemicals, whether singly or in combination.*

This fact is amply demonstrated by the course of our patient. Complete recovery (that is, a gain in strength and weight and disappearance of the acne), did not occur until a full diet supplemented by the entire vitamin B complex was administered. It is possible that the administration of *vitamin B₆ hydrochloride* would have resulted in further improvement. However, we believe that a full diet plus vegex furnishes other factors, both known and unknown, that cannot as yet be supplied by any combination of pure chemical substances.

Treatment.—For the reasons enumerated above, in addition to correction of any condition possibly causing the deficiency, we recommend the following dietary and specific therapy:

1. *Make sure that the diet is adequate in all respects.* The easiest way of doing this is to eliminate all vitamin-free or vitamin-poor foods, such as white bread or crackers, pastries, alcohol, corn syrup, candy, corn starch, polished rice and soft drinks. Yet the diet must be one that the patient can eat, digest and assimilate. For patients who are extremely ill, the diet must be largely restricted to milk, cream, ground liver, puréed legumes, thin whole grain cereals and fruit juices, administered if necessary through the nasal catheter in hourly feedings. Following improvement, or in less severely ill pa-

tients, whole wheat bread or crackers are added. The legumes need not be puréed; other vegetables and raw and cooked fruit are added; and a wider variety of meats are permitted provided that 250 gm. of either liver or pork muscle are included in one of the meals daily.

2. *Supplement the diet by vitamin preparations.* These supplements should include daily 50,000 international units of vitamin A, 200 to 500 mg. of cevitamic acid, and a rich source of the entire vitamin B complex. To insure the adequacy of the entire vitamin B complex, we routinely administer either 20 gm. of vegex, 60 gm. of brewers' yeast, or 30 gm. of aqueous liver extract. We would like to stress that vitamin concentrates, especially those in *pill* or *capsule* form, are possibly *lacking* either quantitatively or qualitatively in one or more of the fractions of the vitamin B complex.

3. *Administer the specific chemical necessary for the specific presenting syndrome in adequate amounts,* erring on the side of wasting the vitamin rather than giving a suboptimal amount.

Thiamin chloride.—If the patient is in circulatory collapse or in severe congestive heart failure, large amounts of thiamin chloride should be given, up to 1000 mg. within the first twenty-four hours. The first dose may consist of 100 mg. intravenously and 300 mg. intramuscularly, with subsequent administration of 200 mg. intramuscularly every three to six hours. During the second twenty-four hours the dosage of thiamin chloride should be reduced to amounts recommended for the less severely ill patients. This latter group can be treated safely, depending upon severity, by administration of 50 to 200 mg. of thiamin chloride daily, preferably given in two doses, intramuscularly. After the patient is saturated with thiamin chloride, the amount of thiamin may be reduced to 10 mg. daily till convalescence is well established. Following convalescence, the balanced diet supplemented by rich sources of the vitamin B complex is sufficient unless a complication exists requiring an unusual amount of vitamin B_1, in which case thiamin chloride should be continued in amounts of 5 to 10 mg. daily.

Riboflavin.—We have administered this chemical in 10 to 30 mg. doses daily by mouth. This procedure has resulted in

rapid clearing of the recognized lesions of this deficiency. Much smaller doses might have sufficed.

Nicotinic acid.—We administer this chemical by mouth in 100 mg. doses for ten doses daily. At first we gave only five doses daily; but occasionally this amount is not optimal, and rarely, it may not even represent a maintenance dose. This large amount is usually necessary for but three or four days. By this time the patient is usually able to ingest a good diet and its supplements, and the dosage is reduced to five times daily, which is continued until convalescence is well established. We then reduce the doses to two daily for approximately one month.

To extremely ill pellagrins, or those subjects having *nicotinic acid deficiency encephalopathy*, we give, in addition, 200 mg. of sodium nicotinate parenterally. This is given in 10 cc. of physiologic saline, one-half administered intramuscularly and the other half intravenously.

BIBLIOGRAPHY

1. Jolliffe, N., and Colbert, C. N.: The Etiology of Polyneuritis in the Alcohol Addict. J.A.M.A., 107: 642 (Aug. 29) 1936.

2. Spies, T. D., Aring, C. D., Gelperin, J., and Bean, W. B.: The Mental Symptoms of Pellagra: Their Relief with Nicotinic Acid. Am. J. Med. Sci., 196: 461 (Oct.) 1938.

3. a. Jolliffe, N., Bowman, K. M., Rosenblum, L. A., and Fein, H. D.: Nicotinic Acid Deficiency Encephalopathy. J.A.M.A., Jan. 27, 1940.

   b. Jolliffe, N.: Effects of Vitamin Deficiency on Mental and Emotional Processes. Res. Publ. Assoc. Nerv. Ment. Dis., 19: 144, 1939.

4. Sebrell, W. H., and Butler, R. E.: Riboflavin Deficiency in Man: A Preliminary Note. Pub. Health Rep., 53: 2282 (Dec. 30) 1938.

5. Jolliffe, N., Fein, H. D., and Rosenblum, L. A.: Riboflavin Deficiency in Man. New Eng. J. Med., Dec., 1939.

6. Spies, T. D., Vilter, R. W., and Ashe, W. F.: Pellagra, Beriberi and Riboflavin Deficiency in Human Beings: Diagnosis and Treatment. J.A.M.A., 113: 931 (Sept. 2) 1939.

7. Sydenstricker, W. P.: Personal communication.

8. Jolliffe, N.: The Diagnosis, Treatment, and Prevention of Vitamin B₁ Deficiency. Bull. N. Y. Acad. Med., 15: 469 (July) 1939.

9. Spies, T. D., and Aring, C. D.: The Effect of Vitamin B₁ on the Peripheral Neuritis of Pellagra. J.A.M.A., 110: 1081, 1938.

10. Goodhart, R., and Jolliffe, N.: The Role of Nutritional Deficiencies in the Production of Cardiovascular Disturbances in the Alcohol Addict. Am. Heart Jour., 15: 569 (May) 1938.

CLINIC OF DRS. IRVING S. WRIGHT AND JOHN B. LUDDEN

DEPARTMENT OF MEDICINE, NEW YORK POST-GRADUATE
MEDICAL SCHOOL AND HOSPITAL, COLUMBIA UNIVERSITY

TREATMENT WITH VITAMIN C
(CEVITAMIC ACID—ASCORBIC ACID)

METHOD FOR COMPENSATING FOR THE FACTOR OF ERROR DUE TO RENAL RETENTION OF VITAMIN C FOUND IN ALL PREVIOUS SATURATION AND BLOOD TESTS*

EXPERIMENTAL studies dealing with vitamin C and its pharmacologic and therapeutic properties continue to be published in great volume. Therapeutic indications have not changed greatly since we reviewed the status of the problem in 1936.[1] Four *general* statements made a year ago, however, may be reiterated since they have been confirmed from many sources:[2]

1. Most patients with scurvy can be cured with ascorbic acid. A very few seem resistant to this substance, but they can be cured with large doses of lemon or other citrous fruits.[3]

2. Increased fragility of the capillaries, when due to vitamin C deficiency, will be restored to normal by the use of this substance, with the same exceptions.[4, 5, 6, 7]

3. Vitamin C deficiency may occur under a great variety of conditions, even when the intake of this substance is apparently adequate. These include *increased* metabolism from infection (with or without fever) or other causes; interference with absorption or utilization because of achlorhydria, colitis, or other intestinal disturbances; and additional factors, concerning which our present knowledge is limited.

4. The proved *indications* for vitamin C therapy depend primarily on the presence, or a danger, of a deficiency of this substance in the patient. This applies whether the primary

problem is clinical or subclinical scurvy or any of the very numerous diseases for which it has been recommended as an important therapeutic aid.

Evaluating Ability to Absorb Vitamin C.—The importance of properly evaluating the ability to absorb vitamin C, the degree of saturation of the body with vitamin C, and the presence or absence of pathologic changes indicating prescorbutic or scorbutic conditions should be obvious as a result of previously published literature. In addition to the above factors we have recently demonstrated that *renal retention* of vitamin C may also occur under certain conditions, especially in the presence of kidney damage.[2, 8] This has been confirmed by Sendroy and Miller.[9]

The ability of an individual to absorb vitamin C from the intestinal tract is, of course, requisite to its normal use. *Achlorhydria,* the too free use of *alkalies, colitis, diarrhea, drastic catharsis* and other important factors militate against this.

We* have recently studied the gastro-intestinal absorption and oral requirements of a number of patients with *chronic diarrhea* of varying degrees of severity. The vitamin C content of stools, obtained from six to twenty-four hours after an oral dose of 1 gm. of ascorbic acid, ranged from 19 to 380 mg. The amount appeared to depend chiefly on the number and character of the stools. When compared with normal values of not over 6 to 10 mg. daily as reported by Abt and Farmer,[21] the potential significance of the loss due to diarrhea is apparent. The oral requirements for the maintenance of saturation for five patients with diarrhea ranged from 150 to 900 mg. daily.

The following procedure may be useful in *determining deficient absorption* from the gastro-intestinal tract:

1. Take a control specimen of blood for determination of the plasma ascorbic acid.
2. Give the patient 1 gm. of ascorbic acid orally.
3. Take blood specimens at the end of one, two and three hours. Whatever the control levels were, a definite rise will be noted in the first hour specimen, with a peak at the second or third hour if the cevitamic acid is absorbed.

* Unpublished data (Wright, I. S., Ludden, J. B., and Bercovitz, Z.).

The *normal blood plasma level* for vitamin C by the method of Farmer and Abt[10] ranges from 0.7 to 1.3 mg. per 100 cc. With the above test it should rise to 1.5–2 mg. or above. Poor absorption will result in slight or no rise. The rise will be less marked in deficiency states than in the presence of saturation. The control blood level will permit due consideration to be given to this factor which in deficiency states is due to rapid storage and utilization by previously deprived tissues.
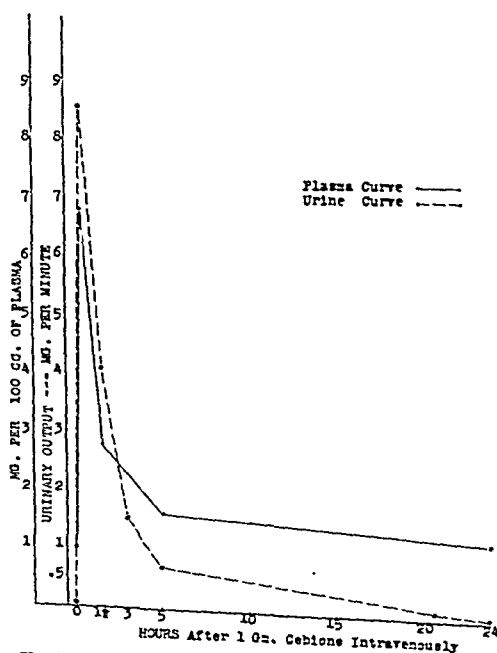
Fig. 96.—Typical curve of vitamin C in the urine and plasma of a normal subject.

Total excretion in 1½ hours — 432.9 mg.
Total excretion in 5 hours — 661.1 mg.
Total excretion in 24 hours — 788.2 mg.

Saturation Tests.—Numerous tests for the degree of saturation of the body with vitamin C have been described. The simplest test and one giving fairly satisfactory information is the study of a *single blood plasma specimen* for vitamin C content.[10, 15] The results of this test, however, may be affected by the dietary intake or deficiency of vitamin C during the pre-

ceding twenty-four to forty-eight hours, and also by renal re-
tention if present, and hence may give an erroneous picture of
the degree of saturation of the body tissues as a whole.[1-2, 11-12]

Twenty-four hour *urine studies* are informative if the speci-
mens are carefully collected, stored, and analyzed, but are
generally impractical because of difficulties in collection and
the deteriorative tendencies of vitamin C.

To compensate for these disadvantages, *oral test dose*
methods were suggested, but these have proved unsatisfactory
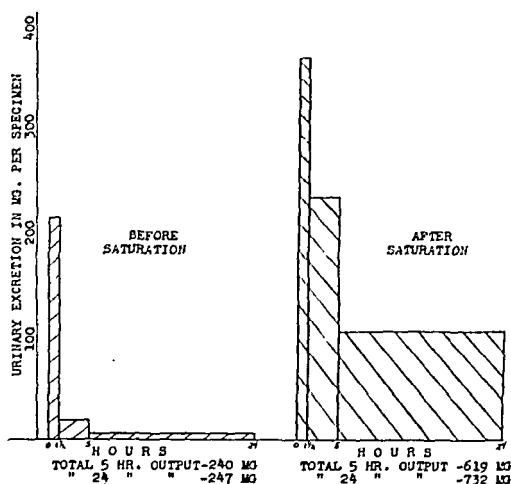
Fig. 97.—Comparison of the twenty-four-hour excretion of cevitamic acid,
after an intravenous injection of 1 gm. cebione, before and after saturation.
This patient received 4600 mg. cebione orally during the five days between
tests. Ninety-seven per cent of the twenty-four-hour output was excreted in
the first five hours before saturation as compared with 84 per cent after
saturation.

owing to the uncertainty of absorption as indicated above.
We therefore suggested[1, 13] in 1936 an *intravenous* five-hour
test dose method which has proved quite satisfactory both here
and abroad.[11] A 1 gm. dose of ascorbic acid is used, since the
factors of error in analysis and due to the preceding dietary
regimen are increased with the use of the smaller doses (100-
300 mg.) which have been suggested by others. The objection
that the 1 gm. dose results in excessive excretion of the vitamin

in the urine does not hold, since we have had returns of as low
as 36 mg. in five hours in scorbutic patients. All excretion
tests are based on the increased output in the urine as satura-
tion is approached, assuming the function of kidney to be
normal.[14, 16, 17, 18, 19]

We did find, however, as above mentioned, that this test,
in common with all other saturation tests and also the blood
plasma levels, could give erroneous results when *renal reten-
tion* of vitamin C existed.[2, 8] Under these circumstances, after
the injection or ingestion of vitamin C, following the initial rise
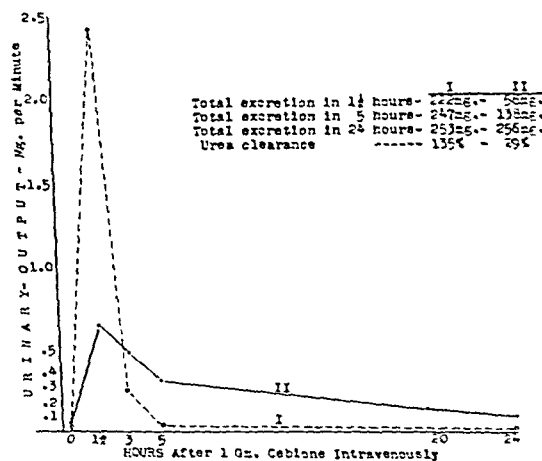
Fig. 98.—Comparison of the excretion curve of a patient with impaired
vitamin C excretion with that of a patient with normal renal function and a
similar vitamin C deficiency.

instead of the prompt drop in the plasma level within from
two to five hours with an accompanying rise in the excretion in
the urine we find a prolonged elevation in the blood plasma
level and a retarded excretion of the vitamin C. Interestingly,
however, if followed for a full twenty-four-hour period, the
excretion of the vitamin C takes place in proportion to the de-
gree of saturation of the patient. Hence, once more the twenty-
four-hour excretion becomes important.

Because of the impracticability of a 24-hour test we
undertook to find some technic by which a shorter test could
be used and yet compensate for the error due to renal reten-

tion. It was finally found that a definite relationship existed between the proportion of the total vitamin C excreted in five hours which was excreted in the first one and one-half hours, and the proportion of the total vitamin C excreted in twenty-four hours which was excreted in the five-hour period.[14] By

TABLE 1

RESULTS OF TWENTY-FOUR HOUR VITAMIN C EXCRETION TESTS AFTER THE INTRAVENOUS INJECTION OF 1 GM. CEVITAMIC ACID

Sub-ject.	Vit. C diet.	Control plasma mg. %	Actual urinary output.					Pre-dicted 24 hr. output‡ mg.	Percent-age error.§
			1½ hr. mg.	5 hr. mg.	24 hr. mg.	1½–5 hr. Exc. %*	5–24 hr. Exc. %.†		
1	Exc	0.98	432.9	661.1	788.2	65.4	83.9	779.9	1.04
2	Exc	1.17	423.0	689.4	784.8	61.3	87.8	842.0	7.26
3	Exc	....	359.2	603.2	757.0	59.5	79.6	747.8	1.21
4	Exc	1.32	414.0	637.0	737.6	65.0	86.3	754.2	2.25
5	Exc	1.41	377.8	618.8	732.3	61.1	84.5	757.3	3.27
6	Good	0.78	352.0	562.9	716.8	62.5	78.5	679 6	5.18
7	Good	0.95	267.1	483.4	674.8	55.2	71.6	626.8	7.10
8	Good	0.58	327.4	510.8	633.4	64.1	80 6	609.0	3.85
9	Good	0.91	313.6	522.3	624.5	60.4	83.6	644.6	3.21
10	Good	0.41	304.0	479.5	620.5	63.4	77.3	574.8	7.37
11	Good	0.95	178.2	380.1	602.4	46.8	63.1	555.6	7.76
12	Good	0.57	218.5	430.1	585.2	50.8	73.7	590.4	0.89
13	Fair	0.50	341.9	479.5	526 8	71.3	91.0	544.1	3.28
14	Fair	0.61	265.5	418 7	497.8	63.4	84.0	502.5	0.94
15	Good	0.79	266.2	418.2	481.1	63.6	86.9	500.3	4.44

Low normal level.

Sub-ject.	Vit. C diet.	Control plasma mg. %	Actual urinary output.					Pre-dicted 24 hr. output‡ mg.	Percent-age error.§
16	Fair	0.49	87.7	239.8	443.7	36.7	54.1	458.9	3.42
17	Fair	0.22	290.4	358.2	374.0	81.0	95.7	386.3	3.28
18	Poor	0.17	286.0	311.1	315.9	91.9	98.4	321.9	1.90
19	Fair	0.30	234.4	269.4	283.4	87.0	95 1	283.7	0 05
20	Fair	0.31	75.5	179.1	271.1	42.1	66 1	289.0	6.62
21	Poor	0.26	237.4	262.5	268.7	90.4	97 6	273.0	1.60
22	Fair	0.26	245.4	263 3	265.3	93.4	99 2	271 3	2 26
23	Fair	0.59	58.3	138 5	256 4	42 1	54 3	223.9	12.67‖
24	Fair	0.33	221.9	247.0	252.3	89.9	97 9	257.4	2.02
25	Poor	0.13	216.6	240 0	246 4	90.3	97.7	249.8	1.33
26	Poor	0 16	53 5	143 6	237 1	37 2	60.5	268 3	13.20‖
27	Poor	0.17	194.7	211.6	221 7	92.0	95.4	218 8	1.31
28	Poor	0.09	88.3	103 3	108.7	85 6	95.0	109 4	0.65
29	Poor	0.18	97.4	97.6	97.9	99.8	99 8	98.6	0.71

Mean 3.12 ± 2.2

* Percentage of the 5 hour output excreted the first 1½ hours.
† Percentage of the 24 hour output excreted the first 5 hours.
‡ Predicted 24 hour output according to the formula in the text.
§ Percentage of error of predicted 24 hour output when compared with actual 24 hour output.
‖ Omitted from calculation of mean due to large relative deviation.

analyzing this data from a series of twenty-nine studies and plotting a graph in which the ordinate represented the five-hour to twenty-four-hour percentage relationship and the abscissa represented the reciprocal of the one and one-half hour to five-hour percentage relationship, it was found that the points lay

practically on a straight line, which verified the constancy of this relationship. A paper describing the details of this analysis is being published elsewhere, but the final working formula is as follows:

$$C = \frac{ab}{1.26a - .27b}$$

where c = 24-hour excretion of vitamin C in mg.
a = 1½-hour excretion of vitamin C in mg.
b = 5-hour excretion of vitamin C in mg.

By means of this rather simple formula it is possible to predict the twenty-four-hour urinary output of vitamin C from data obtained from the one and one-half and five-hour specimens. The mean error, when compared with the actual twenty-four-hour output, was only 3.12 ± 2.3 per cent, which is rela-
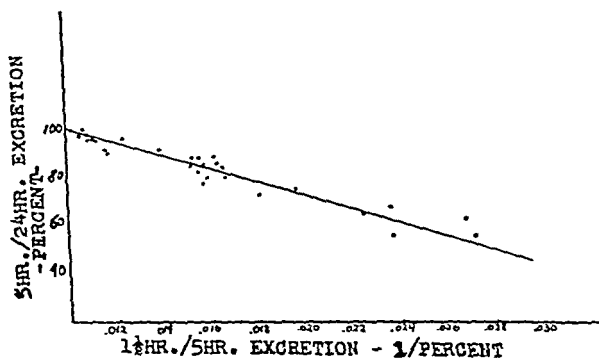
Fig. 99.—The percentage of the twenty-four-hour vitamin C output excreted during the first five hours, after the injection of 1 gm. of cevitamic acid, is plotted against the reciprocal of the percentage of the five-hour output excreted during the first one and one-half hours. The line is calculated from the formula given in the text and the dots represent the actual experimental values.

tively insignificant in comparison with the constant and possible errors of methods of this type of biological chemistry. The *degree* of renal insufficiency or retention of vitamin C has not been found to affect the accuracy of this test and, so far as we know, it is the only method thus far devised which compensates automatically for this factor. This should be qualified by one exception: two patients in extreme uremia have

not given satisfactory results. Such patients may be, of course, readily recognized and do not primarily constitute vitamin C nutritional problems. Of interest is the fact that several patients have been found who show a renal retention of vitamin C even though the usual renal function tests, including blood nonprotein nitrogen and urea nitrogen, urea clearance tests, etc., gave normal results. It should be noted that these patients were all over sixty years of age and were under treatment for extensive peripheral arterio- and arteriolar sclerosis. One might well question the status of their renal vessels.

Technic of Saturation Test.—The following technic is therefore suggested as a modification of the original[13] five-hour saturation test[14]:

Have the patient omit breakfast on the morning of the test. Immediately after the patient has voided and discarded the preliminary urine, inject 1 gm. of ascorbic acid in 10 cc. of physiologic solution of sodium chloride intravenously. Collect urine specimen No. 1 exactly one and one-half hours after the injection and specimen No. 2 exactly five hours after the injection. Titration using a modification of Tillman's method[8–13] should preferably be done immediately after each collection but, if necessary, the first specimen may be preserved as outlined previously[1] and titrated at the end of the test.

Using the values obtained from specimen No. 1 (a), and the sum of the specimens Nos. 1 and 2 (b), the predicted twenty-four-hour excretion (c) may be calculated according to

the formula: $C = \dfrac{ab}{1.26a - .27b}$. The predicted twenty-

four-hour excretion may be termed the *saturation index.*

The reason for devoting so much time and thought to the working out of methods to determine the status of a patient as to vitamin C saturation is obvious. *Treatment cannot be intelligently undertaken without this knowledge.*

Evaluation of Pathologic Changes Resulting from Vitamin C Deficiency.—It is likewise important to know whether pathologic changes have taken place as a result of prolonged vitamin C deficiency. This cannot be evaluated by chemical tests. In the later stages of scurvy, symptoms and signs develop which point to the diagnosis, but long before such

a stage is reached it is possible to determine early changes by means of *capillary fragility tests*. These may be roughly divided into those using a tourniquet method, with increased pressure within the vessels, and those using suction from without, in the form of suction cups. The former method appears to be more satisfactory and requires no special equipment. A modification of Gothlin's method has previously been described and is now widely used.[5, 6]

Like all such tests the weakness in this approach lies in the attempt by some workers to "over-interpret" their results. Normally, fewer than ten petechiae should be produced in a circle 2.5 cm. in diameter after fifteen minutes of tourniquet pressure halfway between the systolic and diastolic blood pressure. A border zone of from ten to twenty petechiae exists and above twenty is considered pathologic. Small differences are probably not important, but there can no longer remain any doubt that readings from thirty upward are definitely pathologic.

It should be remembered that in addition to scurvy, numerous other conditions can produce this phenomenon: *poisons*, such as arsphenamine and carbon monoxide: *toxins* from scarlet fever, diphtheria and septicemias: and *metabolic products* associated with anemia, acetonemia, menstruation and other conditions. Decreased fragility has been noted in secondary anemias although there was chemical evidence of severe vitamin C deficiency. This may be due to exudation of serum through the broken capillaries rather than the visible red blood cells; more often, the pathologic changes have not yet taken place.

When vitamin C alone produces prompt reduction in the numbers of petechiae and when the vitamin C saturation or blood studies are closely correlated, there can be no question as to the relationship and importance of this finding. The routine use of this simple test would be of value to every practitioner of medicine. An abnormal finding warrants a complete investigation as to cause and not infrequently results in uncovering a hitherto unsuspected case of preclinical or clinical scurvy.

Scurvy Not a Rare Disease.—One of the great delusions under which the medical profession has been laboring for many years is that scurvy is a rare disease confined to the poor.

This is far from the truth. The disease is common, at least in its milder forms, even among those in the upper economic stratum of society. We have recently reported six cases of this disease in one family of this type.[20]

Aside from poverty the *causes* have been a distaste for citrous fruits and other foods containing large amounts of vitamin C; allergic and gastro-intestinal sensitivity to such foods; diets prescribed by physicians in treating peptic ulcers, colitis, urticaria and other conditions; faddists' diets and winter diets; and inadequate absorption of vitamin C when taken by mouth and increased requirement because of metabolic dysfunction (including fever, etc.). Cases falling into any of the above groups constitute a definite indication for the supplementary use of ascorbic acid whenever citrous fruit juices (or other natural sources) cannot be used or prove inadequate.

Indications for Vitamin C Therapy.—The present status in reference to the employment of vitamin C therapy remains today as predicted in 1936[1]: "the debatability of its use in any condition seems to be in reverse proportion to our certainty of the relation of that condition to vitamin C deficiency."

For scurvy and prescorbutic conditions, vitamin C remains the only specific therapy. Our conception of the *symptoms* of this condition has, however, broadened greatly: *Warning signals* include: weakness; anemia; a feeling of heaviness, pains in the legs and elsewhere; dizziness; nausea; dyspnea; bleeding from nose, mouth, throat, spongy gums, rectum and bladder; purpuric spots, including hemorrhages under the toe nails and the sclerae; brawny pigmented edema of the lower legs; and other bizarre manifestations, practically all of which depend directly or indirectly on rupture of the blood vessels.

The list of additional diseases for which vitamin C has been recommended is too long to be reviewed in detail here. (See former reviews (1) (6) (21).) We have seen no proof of specific value in blood dyscrasias such as thrombocytopenic purpura haemorrhagica and hemophilia, although occasionally there has been noted an increase in platelet count following its use.

Most workers in this field now agree that in many diseases

with infection present, with or without fever, a marked deficit of vitamin C may occur in spite of a normal intake; such is the case in *pneumonia*,[22, 23, 24, 25] *whooping cough*,[32] and *osteomyelitis*.[33] This should not be construed as proving an etiologic relationship nor a specific curative effect of vitamin C in these conditions. It is, however, logical to replace this deficit as a matter of supportive therapy. Encouraging results have been reported in the treatment of *intestinal tuberculosis* and *diphtheria*,[35, 36] but further work must certainly be carried out to evaluate these claims. Animal studies have been reported suggesting the value of vitamin C in the prevention and treatment of *poliomyelitis*,[37, 38, 39] but conclusive clinical studies have not yet demonstrated the value of this procedure. Recent work in our laboratory failed to demonstrate its value in the treatment of herpes simplex encephalitis in rabbits.[40]

Animal and human studies suggest that there may be a definite relationship between vitamin C deficiency and the *rate of wound healing*.[41, 42, 43, 44, 45, 46] Vitamin C appears to have certain additional qualities, including the stimulation of normal tooth and gum growth, the ability to produce depigmentation as in Addison's disease (and even in the negro to a certain degree), some effect on bodily immunity against certain drug intolerances, and, perhaps protection against experimental anaphylaxis. For a complete review of these attributes the reader is referred to the article by Abt and Farmer.[21]

Dosage of Vitamin C.—Vitamin C should be primarily considered as a *food* rather than as a *medicament*. It is present in ample amounts in natural foods if they are taken in adequate quantities; citrous fruits and tomatoes contribute the largest quantities. The average adult human need for vitamin C for the prevention of scurvy is from 30–60 mg. (600–1200 international units) daily. Fresh orange juice contains 40–60 mg. of vitamin C per 100 cc. so that 200 cc. of orange juice should certainly appear to be ample.

We have, however, encountered a number of patients who will develop scurvy on such a regimen—for one of many reasons such as deficient absorption, utilization, etc. Frequently, intravenous administration of the crystalline vitamin C will solve this difficulty. One of the most unusual cases of this type, recently reported from our clinic,[20] exhibited the follow-

ing phenomena: when given 300 mg. of vitamin C daily practically none was excreted and symptoms of scurvy appeared. On a regimen of 600 mg. daily, the average urinary output was about 50 mg. and no scurvy was observed. On a 1000 mg. dosage, the average excretion was 470 mg., suggesting that the average requirement for the prevention of scurvy in this patient was 550–600 mg. daily. She was followed for seventeen months and relapsed under unusual stress and strain on the dosage of 1000 mg. daily.

The following possibilities in this case suggested themselves by way of explanation:

1. Variations in gastro-intestinal absorption. These were discounted in this case since the twenty-four-hour output was over 500 mg. following an oral dose of 100 mg. The five-hour saturation test returned 500 mg. in five hours.

2. Curious metabolic changes may have affected the utilization of vitamin C.

3. Metabolic phenomena may have changed vitamin C into a non-antiscorbutic substance.

4. Perhaps some deficiency factor other than vitamin C produced the scorbutic-like syndrome and large doses of vitamin C merely compensated for the abnormal endothelial weakness due to this unknown factor.

There is certainly a great factor of safety between the average required dosage and the toxic dose, since we have given as high as 10,000 mg. intravenously in a single dose without untoward effects. Whereas the normal concentration of vitamin C in the blood is from 0.7–1.5 mg., levels of 22.0 mg. have been observed without evidence of toxicity.[47] In general, *larger daily* doses (300–1000 mg.) result in more rapid response. When the patient is depleted, most of the vitamin C is retained and the excretion is low. As the saturation point is approached, the excreted proportion becomes greater and the therapeutic requirement becomes less.

The *dosage for clinical use* may, therefore, range between 30 and 1000 mg. of crystalline vitamin C orally or intravenously. Three to five grams given orally in *divided* doses over a period of from three to seven days have been sufficient to bring most deficient patients into a normal range of saturation.

Saturation may then be maintained with 50–100 mg. daily in patients with normal absorption and utilization. Larger doses will be necessary in patients with increased requirements or impaired absorption from causes mentioned previously. The smaller doses may be given in the form of citrous fruit juice orally unless contraindicated. If the intramuscular route is decided upon, ascorbic acid must be *neutralized* either at the bedside[48] or as a previously prepared solution.[49] The recommended *intramuscular dosage* is 100 mg. once or twice daily as required.

Summary.—"It should never be forgotten that scurvy is a common disease and a common complication, easily missed, easily diagnosed and easily cured."[2]

Scurvy can be cured by the use of synthetic vitamin C, with rare exceptions which appear to require citrous fruit juices. Vitamin C deficiency may occur under a variety of conditions even when the intake is apparently adequate. When this deficiency is sufficiently severe and prolonged, the physical signs of scurvy appear, the earliest being increased capillary fragility. When on a scorbutic basis, increased capillary fragility will respond quickly to vitamin C therapy.

The proved indications for vitamin C therapy still remain the deficiency or danger of deficiency of this substance, whatever the complicating circumstances or diseases associated. Its value in numerous diseases has been discussed.

The status of vitamin C metabolism can be fairly completely determined by means of blood studies, intravenous saturation tests, and capillary fragility tests. A modification of the original five-hour saturation test which compensates for the factor of renal retention of vitamin C is presented.

When lack of chemical facilities prevent complete studies, vitamin C may be safely administered according to the suggestions outlined in this paper.

BIBLIOGRAPHY

1. Wright, I. S.: The Present Status of the Clinical Use of Cevitamic Acid (Ascorbic Acid) (Crystalline Vitamin C). Amer. Jour. Med. Sci., 192: 719 (Nov.) 1936.

2. Wright, I. S.: Cevitamic Acid (Ascorbic Acid; Crystalline Vitamin C): A Critical Analysis of Its Use in Clinical Medicine. Ann. Int. Med., 12: 516 (Oct.) 1938.

3. Elmby, A. and Warburg, E.: Inadequacy of Synthetic Ascorbic Acid as an Antiscorbutic Agent. Lancet, ii, 1363, 1937.

4. Wright, I. S.: Treatment of Adult Scurvy with Crystalline Vitamin C. Proc. Soc. Exp. Biol. and Med., 32: 32, 1934.

5. Schultzer, P.: Studies on Capillary Resistance. Acta Med. Scand., 81: 111; 83: 544; 85: 563; 1934.

6. Wright, I. S. and Lilienfeld, A.: Pharmacological and Therapeutic Properties of Crystalline Vitamin C. Arch. Int. Med., 7: 241, 1936.

7. Dalldorf, G. and Russell, J.: Effect of Cevitamic Acid Injections on Capillary Resistance. J.A.M.A., 104: 1701, 1935.

8. Wright, I. S. and MacLenathen, E.: Vitamin C Saturation—Kidney Retention After Intravenous Test Dose of Ascorbic Acid. Proc. Soc. Exper. Biol. and Med., 38: 55, 1938.

9. Sendroy, J., Jr. and Miller, B. J.: Renal Function as a Factor in the Urinary Excretion of Ascorbic Acid. J. Clin. Invest., 18: 135, 1939.

10. Farmer, C. J. and Abt, A. F.: Ascorbic Acid Content of the Blood. Proc. Soc. Exper. Biol. and Med., 32: 1625, 1935.

11. Portnoy, B. and Wilkinson, J. F.: Vitamin C Deficiency in Peptic Ulceration and Haematemesis. Brit. Med. Jour., 1: 554 (Mar. 12) 1938.

12. Daum, K., Boyd, K. and Paul, W. D.: Influence of Fever Therapy on Blood Levels and Urinary Excretion of Ascorbic Acid. Proc. Soc. Exp. Biol. and Med., 40: 129, 1939.

13. Wright, I. S., Lilienfeld, A. and MacLenathen, E.: Determination of Vitamin C Saturation—A Five-hour Test. Arch. Int. Med., 60: 264, 1937.

14. Ludden, J. and Wright, I. S.: Effect of Renal Retention of Vitamin C on Saturation Tests—A Formula for Compensation of This Factor of Error. Arch. Int. Med., 65: 151 (Jan.) 1940.

15. Wortis, H., Liebmann, J. and Wortis, E.: Vitamin C in the Blood, Spinal Fluid and Urine. J.A.M.A., 110: 1896:1897 (June 4) 1938.

16. Van Eekelen, M.: On the Amount of Ascorbic Acid in Blood and Urine—The Daily Human Requirements for Ascorbic Acid. Biochem. J., 30: 2291, 1936.

17. Lund, H.: Eine Quantitative und Spezifische methode zur Ascorbinsauretitration im Harn und zur Bestimmung des Schwellenwertes. Klin. Wchnschr., 16: 1085, 1937.

18. Faulkner, J. M. and Taylor, F. H. L.: Observations on the Renal Threshold for Ascorbic Acid in Urine. J. Clin. Invest., 17: 69, 1938.

19. Ralli, E. P., Friedman, G. J., and Rubin, S. H.: The Mechanism of Vitamin C Excretion in Man Studied by Simultaneous Vit. C and Insulin Clearances. J. Clin. Invest., 17: 765, 1938.

20. McGovern, T., Gannon, C. F. and Wright, I. S.: Vitamin C Deficiency —Clinical and Therapeutic Problems—With a Case Study of Six Patients in One Family. Amer. Jour. Med. Sci., 197: 310 (Mar.) 1939.

21. Abt, A. F. and Farmer, C. J.: Vitamin C—Pharmacology and Therapeutics. J.A.M.A., 111: 1555 (Oct. 22) 1938.

22. Schroeder, H.: Excretion in Health and Disease. Klin. Wchnschr., 484, 1935.

23. Gauldager, A. and Poulsen, J. E.: Undersglser over C Vitaminud-skellelsen. Hospitalstidende, 78: 1029, 1935.

24. Harde, E., Rothstein, J. A. and Ratish, H. D.: Urinary Excretion of Vit. C in Pneumonia. Proc. Exp. Biol. and Med., 32: 1088, 1935.

25. Gander, J. and Niederberger, W.: Vit. C in the Treatment of Pneumonia. Munchen. med. Wchnschr., 83: 2074, 1936.

26. Abbasy, M. A., Harris, L. J. and Ellman, P.: Vit. C and Infection. Lancet, i, 181, 1937.

27. Heise, F. H. and Martin, G. J.: Ascorbic Acid Metabolism in Tuberculosis. Proc. Soc. Exper. Biol. and Med., 34: 642, 1936.

28. Abbasy, M. A., Grayhill, N. and Harris, L. J.: Vitamin C and Juvenile Rheumatism. Lancet, ii, 1413, 1936.

29. Rinehart, J. F. Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid Arthritis. Ann. Int. Med., 9: 671, 1935.

30. Rinehart, J. F., Greenberg, L. D. and Baker, F.: Reduced Ascorbic Acid Content of Blood Plasma in Rheumatoid Arthritis. Proc. Soc. Exp. Biol. and Med., 35: 347, 1936.

31. Portnoy, B. and Wilkinson. J. F.: Vitamin C Deficiency in Peptic Ulceration and Haematemesis. Brit. Med. Jour., i, 554 (Mar. 12) 1938.

32. Ornerod, M. J. and Von Kauf, B. M.: Further Reports on Ascorbic Acid Treatment of Whooping Cough. Canad. Med. Assoc. Jour., 37: 268, 1937.

33. Abbasy, M. A., Harris, L. J. and Graybill, N.: Vitamin C and Infection. Lancet, i, 177, 1937.

34. Steinbach, M. M., Klein. S. J. and Hirst, A.: Personal communication.

35. Momusen, H.: Remarks Given Before the Medical Society Frankfort. Munchen. med. Wchnschr., 82: 82, 1935.

36. Messer, H.: Beitrag Fir Nebennierenrindentherapie bei diphtherie. Deutsch. med. Wchnschr., 62: 1131, 1936.

37. Jungblut, C. W.: Inactivation of Poliomyelitis Virus in Vitro by Crystalline Vitamin C. Jour. Exp. Med., 62: 517, 1935.

38. Jungblut, C. W.: Attempts at Vitamin C Therapy in Experimental Poliomyelitis. Jour. Bact., 31: 34, 1936.

39. Jungblut, C. W.: Vit. C in Therapy and in Prophylaxis in Experimental Poliomyelitis. Jour. Exp. Med., 65: 127, 1937.

40. Flexner, J., Chassin, M. and Wright, I. S.: Studies with Herpes Simplex Encephalitis in Rabbits—The Therapeutic Effect of Vitamin C, Sulphanilamide, and Pituitary Extract. J. Inf. Dis., 66: 30 (Feb.) 1940.

41. Jeney. A. V. and Korposey, V. V.: Verzogerte Heilung der Haut- und Knochenwunden bei skorbuttieren. Zentralbl. f. Chir., 61: 2836, 1934.

42. Wolback, S. B.: Source of Intracellular Substance in Recovery from Experimental Scorbutus. Am. J. Path., 60: 689, 1933.

43. Aron, H.: Die Nahroschaden des Kindes. Berlin and Vienna, Urban und Schwarzenberg, 103, 1928.

44. Lanman. T. H. and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing. Experimental and Clinical Study. Ann. Surg., 105: 616 (April) 1937.

45. Taffel, M. and Harvey. S. C.: Effect of Absolute and Partial Vitamin

C Deficiency on Healing of Wounds. Proc. Soc. Exp. Biol. and Med., **38**: 418 (May) 1938.

46. Hanke, H.: Experimentelle Untersuchungen uber' Beeiflussung der Knochenregeneration durch Vit. C. Deutsche Ztschr. f. Chir., **245**: 530, 1935.

47. Friedman, G. J., McGoey, C. and Ralli, E. P.: Personal communication. (Quoted by Abt and Farmer, see ref. 21.)

48. Fischer, B. H. and Leake, C. D.: The Parenteral Administration of Cevitamic Acid (Ascorbic Acid) Solution. J.A M.A., **103**: 1556 (Nov. 17) 1934.

49. Lilienfeld, A., Wright, I. S. and MacLenathen, E.: Intramuscular Injection of Ascorbic Acid and Excretion in the Sweat. Proc. Soc. Exper. Biol. and Med., **25**: 184. 1936.

CLINIC OF DR. DONOVAN J. McCUNE

DEPARTMENT OF PEDIATRICS, COLLEGE OF PHYSICIANS AND
SURGEONS, COLUMBIA UNIVERSITY

RECENT ADVANCES IN THE CLINICAL USE OF VITAMIN D AND RELATED COMPOUNDS

ALTHOUGH it is clear that the antirachitic effect of cod liver oil was recognized nearly one hundred years before the beginning of the present century,[1] the history of vitamin D as an identified biologic principle may be said to have begun exactly two decades ago. The narrative divides itself naturally into two chapters[2]:

In 1919 Mellanby reported the successful production of rickets in puppies by means of a diet low in calcium, and the control of the disease with cod liver oil and certain other fats. The same year saw the publication of Huldschinsky's convincing proof of the cure of human rickets by ultraviolet light. In 1922, McCollum, Simmonds, Becker and Shipley announced that the effective agent in cod liver oil was a substance distinct from vitamin A; they suggested that the new principle be called *"vitamin D."* Independently and almost simultaneously (1924), Hess and Steenbock demonstrated that the antirachitic properties of cod liver oil could be imparted to certain foods by subjecting them to ultraviolet irradiation. In the following year, 1925, Hess and Steenbock in America and Rosenheim

[1] *Hess, A. F.: Rickets, Including Osteomalacia and Tetany. Philadelphia, Lea and Febiger. p. 403. 1929.

[2] *Bills, C. E.: The Multiple Nature of Vitamin D. Cold Spring Harbor Symposia on Quantitative Biology. 3: 328, 1935.

* FOOTNOTES AND BIBLIOGRAPHIC REFERENCES.—An effort has been made to cite references of a general character. Those containing the most extensive bibliographic information are marked with an asterisk (*).

and Webster in England showed that the activable substance in foods was closely linked with their sterol fraction. By 1927 the combined efforts of many workers, notably of Windaus, Hess, and Rosenheim and Webster, led to the revelation that the parent substance of vitamin D activity in irradiated foods was a sterol of plant origin, namely, *ergosterol.*

The second chapter[3] commences in 1932 with the crystallization from the mixed irradiation products of ergosterol of a substance known as *calciferol,* which was thought for a time to be the only naturally occurring form of vitamin D. This step was accomplished by an English group headed by Askew and, independently during the same year, by Windaus and his collaborators; the German workers designated the compound *"vitamin D_2."*[4] While these efforts were in progress, Bills was pursuing investigations which led to the conclusion that more than one chemical substance possessed naturally, or could be endowed artificially, with antirachitic properties. During 1930 several workers reported the important observation that whereas rickets in chicks was readily cured by cod liver oil, it was refractory to the action of irradiated ergosterol. In 1934 Waddell demonstrated that the irradiation of the animal sterol, cholesterol, gave rise to a form of vitamin D that was highly effective in chicks. In the following year, 1935, Windaus, Lettré and Schenck identified the precursor of this type of vitamin D as 7-dehydrocholesterol; to the activated substance, dimethyl-dihydro-calciferol, they assigned the designation *"vitamin D_3."* This was isolated in crystalline form by Schenck in 1937. It has been shown to be the principal source of vitamin D activity in the naturally occurring antirachitic substances of animal origin, the most potent of which are fish liver oils; it is presumably the activable substance in human skin. That calciferol and dimethyl-dihydro-calciferol are not the only forms of vitamin D which are encountered in nature may be surmised from the fact that Bills[5] lists eight additional

[3] *Bills, C. E.: Physiology of the Sterols, Including Vitamin D. Physiol. Reviews, **15**: 1 (Jan.) 1935.

[4] Vitamin D_1 was used for a short time to designate a supposedly pure preparation, which was soon recognized to be a mixture of calciferol and lumisterol.

[5] *Bills, C. E.: The Chemistry of Vitamin D. J.A.M.A., **110**: 2150 (June 25) 1938.

artificial products that exhibit varying degrees of antirachitic activity. To name but two, one may mention 22-dihydrocalciferol (*vitamin D_4*) and activated 7-dehydrositosterol (*vitamin D_5*). Fortunately, up to the present time the clinician has been called upon to assess the relative merits of only two of the many possible forms of vitamin D.

Vitamin D_2, calciferol, or plant vitamin D, the crystals of which have a potency of 40,000 U.S.P. units per milligram,[6] is procurable dissolved in propylene glycol to a concentration of about 250 units per drop of solution.[7] Vitamin D_2 is the antirachitic constituent of all preparations of viosterol in oil. These solutions are generally adjusted to a potency of from 200 to 250 units per drop. Viosterol contains small amounts of other irradiation products of ergosterol. Vitamin D_2 is also the form that appears in the milk of cows fed irradiated yeast, the so-called "metabolized" milk, and is sometimes added directly to produce one type of what is known as "fortified" milk.

Vitamin D_3, irradiated 7-dehydrocholesterol, dimethyldihydro-calciferol, or animal vitamin D, in crystalline form also has a potency of 40,000 units per milligram. No solutions that are advertised to contain the crystalline substance and to be entirely free from the by-products of irradiation have yet appeared on the market, although material so described can be obtained for purposes of clinical investigation through the courtesy of one manufacturer.[8] Several preparations marketed as "activated animal provitamin D in oil" have recently become available. The purity of these preparations is presumably comparable with that of solutions of viosterol. Fish liver oils and their concentrates, irradiated milk, milk fortified by the addition of fish oil concentrates, and that produced by feeding irradiated cholesterol, as well as other foods of animal origin such as eggs and butter, are all thought to owe their antirachitic

[6] *Park, E. A.: The Use of Vitamin D Preparations in the Prevention and Treatment of Disease. J.A.M.A., 111: 1179 (Sept. 24) 1938. The International Units and the U.S.P. XI Unit are identical. Both refer to the antirachitic activity in the rat of 1 mg. of the international standard solution of irradiated ergosterol. This has been found equal to 0.025 microgram of calciferol.

[7] Drisdol. The Winthrop Chemical Company.

[8] The Alba Pharmaceutical Company.

potency largely, although not exclusively, to the presence of vitamin D_3.

Inasmuch as highly satisfactory results have been attained in the past by the use of fish oils and their concentrates, viosterol, irradiated foods and the rapidly spreading consumption of vitamin D milk, the isolation of the crystalline vitamins D_2
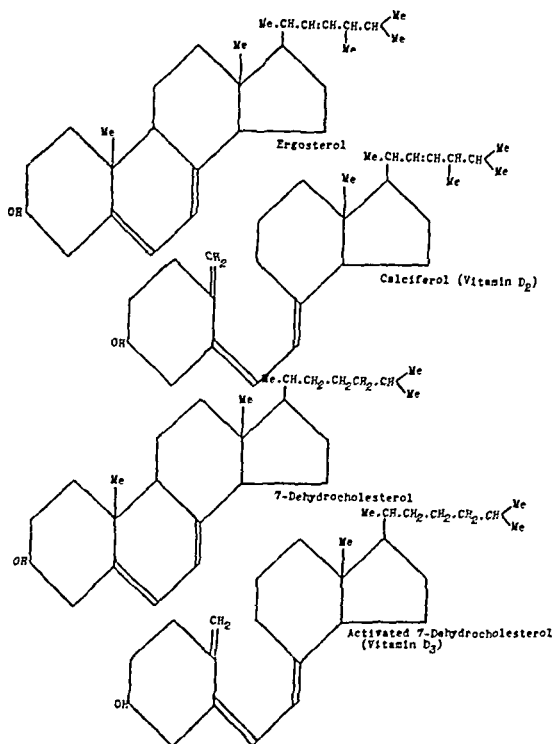
Fig. 100.—Currently accepted structural formulas of vitamins D_2 and D_3 and of their parent substances.

and D_3 does not represent a great boon to the clinician. It has, however, been shown to be important in several respects: First, the advent of pure preparations has stimulated anew the investigation of the relative merits of animal and vegetable vitamin D in human nutrition. Second, these preparations have made possible the use under certain circumstances of dosages of vitamin D much larger than were considered safe in the past.

Third, the researches that resulted in the isolation of pure vitamin D led to a more complete understanding of the transformations that ensue during the irradiation of the parent sterols; one of the fruits of this familiarity is *dihydrotachysterol* (A. T. 10) which, although comparatively untried, promises to be of great value in the treatment of chronic tetany.

As already stated, the first intimation that the protective factors in cod liver oil and viosterol were not identical came from the observation that, although the two were equipotent in the rat, in chicks the former was many times more effective than the latter. Clinical experience suggested that the same inequality of effect existed with reference to human infants.[9, 10] A large number of inquiries into the matter were completed before crystalline vitamin D became available. The most important positive result of these studies was the demonstration that vitamin D is utilized more efficiently when given in *dilute* solution than when administered in concentrated state, and that the effect of equal amounts is greater when ingested in small fractions frequently repeated than when given in a single dose.[11]

With respect to the comparative merits of the two types of vitamin D the studies yielded somewhat contradictory results, although the consensus suggested that vitamin D of animal origin was somewhat—"slightly" is probably a better word—more effective in human beings than vitamin D obtained from the activation of plant sterol. It is disappointing to relate that the more recent investigations inspired by the availability of the crystalline substances have yielded about the same net result.[12] It is evident that the number of uncontrollable biologic variables in this type of inquiry is so great that extremely large numbers of cases studied by extraordinarily scrupulous methods of investigation are required to provide an exact answer.

[9] *Jeans, P. C.: Vitamin D Milk. J.A.M.A., 106: 2066 (June 13); 2150 (June 20) 1936.

[10] *Eliot, M. M. and Park, E. A.: Rickets. Brennemann's Practice of Pediatrics, Vol. I. Hagerstown, Md., W. F. Prior and Co., Chap. 36, p. 98, 1938.

[11] *Jeans, P. C. and Stearns, G.: The Human Requirement of Vitamin D. J.A.M.A., 111: 703 (Aug. 20) 1938.

[12] *Nádrai, A.: Die therapeutische Wert des D₃-Vitamins. Arch. f. Kinderh., 116: 235, 1939.

One way of reducing the number of variables is to make use of identical twins as test subjects. The author[13] has had the opportunity to observe the therapeutic effect of calciferol and dimethyl-dihydro-calciferol in a pair of monozygotic twin girls who suffer from a type of late rickets best described as "refractory" and "relapsing." By employing enormous doses of the two substances it was possible to initiate healing in both patients. Although vitamin D_3 appeared to produce more marked hypercalcemia than vitamin D_2, both affected the serum inorganic phosphorus concentration, the serum phosphatase activity, and the roentgen features of the skeleton identically; in addition, both produced the same degree of hypercalciuria and evidence of renal irritation when the highest level of dosage, 500,000 units daily, was reached. The same phenomena were reproduced in another case of rickets of this type[14]; in this instance the interpretation is more difficult for the reason that the patient served as her own control, being treated first with vitamin D_2, then with D_3. Under these circumstances her state of saturation or depletion could not be termed identical at the beginning of the two periods of treatment.

The three patients referred to represent a clinical situation in which the availability of highly concentrated preparations of vitamin D, free from the by-products of irradiation, is of great advantage. Little is known about the cause of this type of rickets.[15] It is characterized by onset after the first year of life; progessive deformity of the lower extremities; normal serum calcium, decreased serum inorganic phosphorus and moderately increased serum phosphatase activity; absence of distinctly pathologic alterations of the calcium and phosphorus exchange[16]; extreme refractoriness to treatment with the usual therapeutic doses of vitamin D; satisfactory response to daily doses of between 200,000 and 500,000 units; and finally, a consistent tendency to relapse when treatment is withdrawn. The

[13] McCune, D. J.: Proc. Soc. for Ped. Research, May, 1939. Am. J. Dis. Child. To be published.

[14] Unpublished observation.

[15] Albright, F., Butler, A. M. and Bloomberg, E.: Rickets Resistant to Vitamin D Therapy. Am. J. Dis. Child., 54: 528 (Sept.) 1937.

[16] Highman, W. J., Jr. and Hamilton, B.: Calcium and Phosphorus Metabolism in a Case of Intractable Rickets. J. Pediat., 9: 56 (July) 1936.

disease is quite different from rickets due to chronic steator-
rhea, such as is seen in celiac disease and sprue. It differs also
from the types of rickets that complicate liver disease, long-
standing renal insufficiency, renal calcinosis and cystinuria.[6]
It has nothing in common with the DeToni-Fanconi type of
late rickets, which is related to an inborn defect of internal
metabolism that leads to an organic acid acidosis.[17] With the
exception of rickets due to fatty diarrhea, the aforementioned
forms are not significantly benefited by vitamin D, whereas the
type under discussion can be cured, albeit temporarily, if treat-
ment is bold enough. The importance of the recognition of
cases of this type is illustrated by the fact that the three pa-
tients mentioned had all been operated on successfully for the
correction of deformities of the lower extremities, only to have
the distortions recur for lack of adequate treatment.

The availability of chemically pure and highly concentrated
solutions of vitamin D is principally responsible for the success
of Harnapp's method of treating and preventing rickets by the
use of a *single massive dose of vitamin D* (Stosstherapie).[18]
As far back as ten years ago this method had been tested in
America and abroad with results that were inconsistent and not
too promising; further trial was restricted by the lack of po-
tency and the impurity of the material then procurable. Follow-
ing Harnapp's reintroduction of the procedure it has gained
rapid popularity in Europe; its application has been extended
to include the oral and parenteral use of crystalline vitamin D
in the prevention and treatment of rickets and the cure of
tetany, both in full-term and in premature infants.[19, 20] The
dose most commonly employed is 15 mg. (600,000 units) of
either D_2 or D_3 with little regard for age. The amount in-
jected parenterally is smaller; the optimum dose has not yet
been determined.

[17] McCune, D. J., Mason. H. H. and Clarke, H. T.: Late Rickets with
Glycosuria and Organic Acid Acidosis. Tr. Am. Pediat. Soc. Am. J. Dis.
Child., 58: 675 (Sept.) 1939.

[18] Harnapp. G. O.: Rachitisbehandlung durch einmalige Verabfolgung von
Vitamin D₂. Mschr. f. Kinderh.. 66: 318, 1936.

[19] *Braulke. H.: Die Indikationen der Rachitisbehandlung mit einmaliger
Dosis von Vitamin D₂ (Vitaminstoss). Ztschr. f. Kinderh., 59: 18, 1937.

[20] *Vollmer, H.: Treatment of Rickets and Tetany with a Single Mas-
sive Dose of Vitamin D. J. Pediat.. 14: 491 (April) 1939.

The prophylactic effect of this treatment is said to last several months. Gratifying results are claimed in the *prevention of rickets in premature infants.*[21] Therapeutically, the onset of healing of rickets is accelerated, becoming apparent within a few days, although the time required for complete healing is not strikingly shortened. Excellent results are claimed in *infantile tetany.* Usually the danger of spasm is obviated within three or four days; the occasional persistence or recurrence of spasms during this period suggests the advisability of combining the treatment with small doses of calcium and the use of sedatives. The method is recommended for cases in which the presence of serious respiratory infection demands that accompanying rickets be healed without delay; also in situations in which the mother cannot be depended on to carry out medical recommendations. The parenteral route is less open to accidental errors of dosage brought about by vomiting, diarrhea or failure of absorption.

Although German pediatrics has apparently taken up Harnapp's suggestion with enthusiasm, American reception has been less warm; the difference in attitudes is doubtless due to the much greater prevalence and seriousness of rickets in Germany than in the United States. The published reports indicate that the method is almost devoid of danger. However, it is not to be recommended unless some special indication exists and then only when the patient can be *kept under observation.*

The irradiation of ergosterol results in a series of transformations which can be represented as follows[5]:

Ergosterol
↓
Lumisterol
↓
Tachysterol
↓
Calciferol (D₂)
↓
Substance 248 (Toxisterol)   ?
↓
Suprasterol I   Suprasterol II
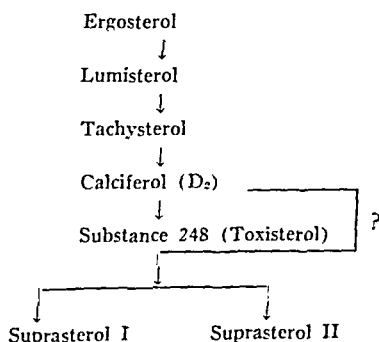
[21] Windorfer, A.: Zur Rachitisprophylaxe bei unreifen Kindern mit dem Vitamin D-Stoss. Mschr. f. Kinderh., 75: 124, 1938.

If, instead of ergosterol, 7-dehydrocholesterol is subjected to irradiation a series of homologous compounds is formed, all of which differ from the ergosterol derivatives in the possession of one less methyl group; in place of calciferol, dimethyl-dihydro-calciferol (D_3) is formed.[22]

It was to the unrecognized presence of some of these by-products of activation, known collectively as the "Calcinose-faktor," that the early supplies of *Vigantol*, the German concentrate, owed their harmful effects. After extensive investigation Holtz[23] announced in 1934 the preparation of dihydro-tachysterol, a derivative of tachysterol that was peculiarly effective in controlling tetany. The value of A. T. 10 (anti-tetanisches Präparat, Nummer 10) in *hypoparathyroid tetany* has been confirmed in Europe and in this country.[24] The daily administration by mouth of less than 1 cc. of this substance together with relatively small amounts of calcium produces highly satisfactory relief of the symptoms of tetany due to lack of parathyroid secretion; it obviates the need for large doses of calcium, acidifying salts, intravenous medication and repeated injections of parathyroid extract—all of which were required in severe cases before the advent of the new agent. Furthermore, patients do not become refractory to dihydro-tachysterol as they often did to parathyroid extract. The use of A. T. 10 carries an element of danger: Safety requires frequent determinations of serum calcium until the proper daily dose is worked out. Although chronic tetany can also be controlled by the administration of large doses of vitamin D,[25] the mode of action of the two substances[26] makes dihydrotachysterol a more logical and probably a safer choice.

In conclusion, *a word of warning is in order:* The sub-

[22] Schoenheimer, R.: Personal communication.

[23] *Pickhardt, O. C. and Bernhard, A.: The Treatment of Postoperative Tetany with Dihydrotachysterol. Ann. Surg., 108: 362 (Sept.) 1938.

[24] MacBryde, C. M.: The Treatment of Parathyroid Tetany with Dihydrotachysterol. J.A.M.A., 111: 304 (July 23) 1938.

[25] Klatskin, G.: On the Actions of Crystalline Vitamin D_2 (Calciferol) in Chronic Parathyroid Tetany. J. Clin. Investigation, 17: 431 (July) 1938.

[26] *Albright, F., Bloomberg, E., Drake, T. and Sulkowitch, H. W.: A Comparison of the Effects of A. T. 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism. J. Clin. Investigation, 17: 317 (May) 1938.

stances that have been discussed are all highly potent; hence it is not surprising that they possess the capacity for harm. This was manifested concretely by the original German experience with Vigantol, an experience that has been confirmed repeatedly whenever large doses of vitamin D have been used indiscriminately. The recent report by Ross and Williams[27] of four cases of vitamin D poisoning in infants illustrates the differences of tolerance and susceptibility that one may expect to encounter and also points to the danger that lies in the practice of gaging the dose of vitamin D in terms of *drops* rather than in terms of the universally comparable *international* or *U.S.P. unit.*

[27] Ross, S. G. and Williams, W. E.: Vitamin D Intoxication in Infancy. Tr. Canadian Soc. for the Study of Dis. of Child., Am. J. Dis. Child., 58 1137 (Nov.) 1939.

CLINIC OF DR. ADE T. MILHORAT

FROM THE DEPARTMENTS OF MEDICINE, PSYCHIATRY AND
PHARMACOLOGY OF THE CORNELL UNIVERSITY MEDICAL
COLLEGE, THE RUSSELL SAGE INSTITUTE OF PATHOLOGY
AND THE NEW YORK HOSPITAL, NEW YORK.

RECENT ADVANCES IN THE THERAPY OF DISEASES OF MUSCLE

IN recent years several noteworthy advances have been made in the therapy of diseases of muscle. As a result, the prognosis in cases of myasthenia gravis has been improved appreciably, and patients with myotonia congenita and familial periodic paralysis can be relieved, at least in a large measure, of the functional defects of their condition. It should be remembered, however, that despite our better understanding of the management of these patients, most of the major problems in muscular disease have remained unsolved. The etiology of practically all of these disorders is still obscure, and the treatment of most of them is still unsatisfactory. In the past few years, however, the diseases of muscle have engaged the attention of workers in biochemistry, nutrition, physiology and pathology. Paralysis and muscular wasting of nutritional origin in animals are being studied carefully, and extensive investigations of the metabolic changes occurring in patients with various types of muscular disorders are being made. Moreover, almost as rapidly as newly discovered vitamins become available, clinical studies are made to determine whether they have any therapeutic effect in the various muscular disorders. It therefore seems not unreasonable to expect that in the next decade more advances in the therapy of these conditions will be made than in any decade in the past.

The following discussion includes the most important advances made in the therapy of diseases of muscle during the past few years:

MYASTHENIA GRAVIS

Prostigmin and Eserine (Physostigmin).—The discovery by Walker that the administration of eserine and prostigmin to patients with myasthenia gravis is followed by definite improvement in muscular function was an important advance in the treatment of this condition. Both eserine and prostigmin depress the activity of the choline-esterase and thereby decrease the rate of hydrolysis of acetylcholine, which according to the studies of Dale and his co-workers is liberated when cholinergic nerves are stimulated. The administration of eserine and prostigmin therefore produces effects similar to those seen after stimulation of cholinergic nerves. For these reasons, and the fact that these drugs often have a dramatic effect on the muscular symptoms, some workers believe that the defect in myasthenia gravis is either a subnormal production of acetylcholine or an increased activity of the choline-esterase. However, experimental evidence in support of either view is lacking. In fact it appears that the choline-esterase activity in myasthenia gravis is not unusual. Both McGeorge and Milhorat found the activity of the serum choline-esterase in myasthenia gravis to be of the same order as that seen in patients without this condition. Moreover, spontaneous changes in the symptoms in myasthenia gravis were observed to be unassociated with any change in the esterase activity.

In spite of our lack of knowledge regarding the nature of the defect in myasthenia gravis, however, it is generally agreed that prostigmin is a valuable drug in the treatment of the disease. The use of eserine is limited definitely because of the undesirable side-effects. I found that when prostigmin and eserine were given in doses that produce similar inhibitory effects on the choline-esterase activity, the effects on voluntary muscle and other structures differed widely. When prostigmin was given, the effects on voluntary muscle, as shown by improvement in muscular function, appeared earlier, were of greater magnitude, and persisted longer than when eserine was given. With the dosages employed, prostigmin had satisfactory therapeutic effects on the muscles without appreciable side-effects. On the other hand, the administration of eserine was followed by considerable dizziness, sweating, abdominal cramps, nausea, and vomiting. Whenever eserine was admin-

istered, atropine usually was required for relief from these un-
desirable side-effects.   Furthermore, prostigmin can be given
satisfactorily by mouth, whereas eserine must be administered
parenterally.

Dosage of Prostigmin.—Prostigmin can be given either by
subcutaneous injection or by the oral route.   Much larger doses
are required when the oral route is employed; usually 15 mg.
of the drug when given by mouth produce the same effects as
0.5 mg. administered subcutaneously.   The subcutaneous ad-
ministration of adequate amounts of the drug is followed in
most instances by improvement in symptoms within a period
of a few minutes.   When the drug is given orally, effects come
on much more slowly; usually twenty minutes are required for
the earliest effect to be observed.   In both instances the effects
last for a few hours and then subside gradually, and the condi-
tion of the patient returns to its previous status.

Patients who are slightly or moderately ill require about 15
mg. orally three or four times daily.   On this regimen, most
patients experience a definite improvement in muscular weak-
ness and fatigability.   Doses larger than those necessary to
induce satisfactory improvement should be avoided for the fol-
lowing reasons: (1) large doses of prostigmin often enable the
patient to engage temporarily in excessive activity with the
result that exacerbation of symptoms usually occurs after a
day or two; (2) large amounts of the drug make the muscle
more refractory to cholinergic stimulation.   Adequate rest and
judicious restriction of activity still form an important part of
the treatment of patients with myasthenia gravis.

Among the several factors that often decrease the effects of
prostigmin are *muscular activity, infection,* and *menstruation.*
It can be shown in many instances that all these factors render
the muscle more refractory to cholinergic stimulation.   The
treatment of patients seriously ill with myasthenia gravis is
still unsatisfactory.   In such patients, progressively increasing
amounts of prostigmin may be needed to maintain function of
the respiratory muscles.   In many instances the muscles be-
come more and more refractory to stimulation until the re-
sponse is so small and transient that respiration fails.   In these
cases the use of a respirator is necessary.   It appears that the
satisfactory management of such patients must await a clearer

understanding of the nature of the defect in myasthenia gravis.

Ephedrine.—The therapeutic effect of this drug in myasthenia gravis was first demonstrated by the careful observations of Edgeworth. Ephedrine is of considerable value in many instances. The *smallest* dose giving a satisfactory therapeutic effect should be employed. Larger doses often induce headache, tachycardia and an increase in muscular symptoms. Usually, amounts of the order of 10 mg. of ephedrine sulfate given by mouth two or three times daily are sufficient. The mode of action of the drug in myasthenia gravis is not known.

Guanidine.—Guanidine increases the response of muscle to cholinergic stimulation. Minot and her co-workers introduced the drug in the treatment of myasthenia gravis, and several investigators subsequently confirmed the observation on the satisfactory effects of guanidine in this condition. The drug may be given either by mouth or by subcutaneous injection. The use of guanidine appears to be definitely more limited than that of prostigmin. When guanidine and prostigmin are given together, the therapeutic effects of the two are additive; no synergistic effect has been demonstrated. The side-effects, such as a sensation of tingling of the tongue, observed occasionally when large doses are administered, can be abolished or prevented by atropine.

Amino-acetic Acid (Glycocoll).—Amino-acetic acid, the simplest of the amino acids, has been observed by many workers to increase the functional capacity of the muscles in myasthenia gravis. The most important and extensive studies on the use of amino-acetic acid in this condition are those of Boothby. The large number of patients studied by Boothby had less muscular disability and lived much longer, on the average, than patients who did not receive this form of therapy. The amount usually given is about 25 gm. daily. This is taken in divided doses and must be continued over long periods of time.

PROGRESSIVE MUSCULAR DYSTROPHY

The treatment of progressive muscular dystrophy still remains unsatisfactory. The use of *amino-acetic acid* is of some value in certain instances. The patients who derive benefit from the use of amino-acetic acid usually are those in whom

the disease appears relatively late in life. In such patients the progression of disability usually is slow and the disease process appears to be more readily affected by treatment. Unfortunately, progressive muscular dystrophy develops in most patients during the first or second decade of life. In these patients, who represent the greatest number of those with the disease, the muscular disability progresses more rapidly. Up to the present time no really effective therapy has been found. In a few cases the continued administration of amino-acetic acid appears to delay the progress of the disease.

The clinical application of the information yielded by experiments in nutritional dystrophy in animals have been disappointing. Continued parenteral administration of various vitamins has been without effect on the muscular disability of patients with dystrophy. The vitamins studied have included alpha-tocopherol (vitamin E), cevitamic acid, riboflavin and vitamin B_6.

MYOTONIA CONGENITA

Quinine.—Wolf and Kennedy made the interesting observation that quinine administered to patients with myotonia congenita decreases or abolishes entirely the inability of the muscles to relax promptly after an initial forceful contraction. Often as little as 0.3 gm. of quinine sulfate given by mouth three times daily will relieve the patient completely of the functional defect of the muscles. After the drug has been taken for periods of a few months, usually the effect on the muscles gradually diminishes. However, if the drug is stopped for a few weeks, renewed administration is again followed by definite effects on the muscles. The effect of quinine in myotonia congenita most probably is related to its known pharmacologic actions. Quinine reduces the effects of cholinergic stimulation on striated muscle and decreases the effects of acetyl-beta-choline and of vagal stimulation on the heart.

PARALYSIS AGITANS

Quinine.—I have observed that the muscular rigidity in this condition often is reduced significantly by the administration of quinine. In certain instances, however, the appearance of side-effects, such as buzzing in the ears and dizziness, does

not permit the use of doses large enough to affect the muscular rigidity. After quinine has been taken for periods of several weeks, the muscular effects gradually diminish. If the drug is stopped for a few weeks, the effects on muscular rigidity usually are apparent again when administration is resumed.

FAMILIAL PERIODIC PARALYSIS

Potassium Chloride.—Aitken, Allott, Castleden and Walker observed an abnormally low level of serum potassium in a patient with familial periodic paralysis during paralytic attacks. Administration of potassium chloride by mouth increased the serum potassium level and abolished the paralysis. They concluded that the lowering of potassium concentration either blocks neuromuscular transmission or inhibits the contractile response in the muscles affected.

Similar observations were made by Gammon. However, it has been shown by Gammon and others that paralysis can occur even when no decrease in the serum potassium level can be demonstrated. Moreover, the administration of 5 gm. of potassium chloride by mouth occasionally can abolish the paralysis without raising the level of serum potassium appreciably in instances where the level is abnormally low. Gammon is of the opinion that the effect of potassium in relieving a paralytic seizure without raising the lowered level of serum potassium can be explained on the basis of direct diffusion of the administered potassium into the muscles. Stewart, Smith and Milhorat have observed alterations of the electrocardiogram and a lowered level of serum potassium during the paralytic phase. Administration of 4 gm. of potassium chloride improved the electrocardiographic changes and the muscular paralysis without changing the serum potassium level. However, the additional administration of potassium chloride sufficient to raise the serum potassium level was followed by complete disappearance of muscular disability and of abnormal electrocardiographic findings.

The avoidance of agents that lower the serum potassium level (epinephrine, insulin, large amounts of sugar) and the administration of potassium chloride usually prevents paralytic seizures in patients with familial periodic paralysis.

AMYOTROPHIC LATERAL SCLEROSIS

Wechsler recently observed definite improvement in two patients following the administration of alpha-tocopherol (vitamin E). This finding has not been confirmed by any other worker and I have never seen improvement in amyotrophic lateral sclerosis following the use of alpha-tocopherol even when the vitamin was given for periods of several months. Further studies on the possible use of the vitamin in this condition are needed.

DERMATOMYOSITIS

Patients with dermatomyositis often have as much muscular wasting as is seen in progressive muscular dystrophy. Milhorat, Weber, and Toscani made extensive investigations in two cases and observed clinical and chemical improvement when wheat germ was given in amounts of about 100 gm. daily for periods of several weeks. Although patients with this condition sometimes improve spontaneously, the findings suggest the importance of wheat germ in the treatment of this condition.

CLINIC OF DR. ROBERT C. PAGE AND
EDMOND G. THOMAS, B.A.

NEW YORK POST-GRADUATE HOSPITAL

THE LOCAL APPLICATION OF RUSSELL VIPER VENOM FOR THE CONTROL OF HEMORRHAGE

THE serpent has occupied an important position in religion and medicine since the earliest times. Symbolic evidence of this fact survives in the royal headgear of the Pharaohs, the stone carvings of the Aztec temples, and in the winged, snake-twined staff, or Caduceus, which was the Roman symbol for healing and which has been chosen as the emblem of the medical profession. The appearance of the snake in scientific medicine is a recent development.

In 1903, Lamb and Hanna[1] investigated the venom of Vipera russellii, or Russell viper. (This snake is native to India where it is called the "Daboia," or "Tic Polonga.") The experiments indicated that Russell viper venom possessed a powerful coagulant action for whole blood or plasma. Its effect on decalcified plasma was relatively weak. Toxic action upon injection was confined to intravascular clotting. In a subsequent report[2] on the same subject, Lamb and Hanna stated that should the quantity of poison injected not be sufficient to cause this clotting, a negative phase of marked diminution of blood coagulability supervenes. This effect could be demonstrated only *in vivo*. These findings were closely similar to those of Wooldridge,[3] who used tissue extracts, and of Martin,[4] who employed the venoms of certain Australian Elapine snakes.

Action.—There has been ample confirmation[5, 6, 7, 8, 9, 10] of the coagulant action of Russell viper venom on whole blood or recalcified plasma, but its effects on citrated blood or plasma have been disputed. Definite coagulant power has been re-

ported by certain investigators,[6, 7, 8, 12] while others have obtained negative or variable results.[5, 10, 11]

Arthus[5] noted that Russell viper venom did not clot peritoneal transudates, purified fibrinogen solutions, or blood to which oxalates or fluorates had been added; nor did it yield a thrombin-like substance after incubation in the presence of ionic calcium. However, it accelerated the coagulation of recalcified blood in a manner similar to that of tissue extracts. These phenomena led Arthus to conclude that the action of the venom was like that of thromboplastic substances.

Houssay and Sordelli[6] found that the venom greatly accelerated the production of thrombin in a mixture of centrifuged, oxalated plasma, serum (containing prothrombin), calcium ions and tissue extract. In the absence of tissue extract no thrombin was formed. Thus it appeared that the venom facilitated the thromboplastic action of tissue extracts.

Ganguly[10] reached much the same conclusion with reference to the thromboplastic action of platelets. It was noted that no clot was produced by incubation of prothrombin and fibrinogen in the presence of calcium ions; however, the addition of platelets yielded a clot in forty-three minutes, while when both platelets and venom were added, the clot formed in eighteen minutes. Ganguly states that these findings led him to believe that "Daboia venom itself does not possess any of the properties of converting prothrombin to thrombin or fibrinogen to fibrin. It does not play the part of calcium either, but only acts cytologically on the platelets of the blood, enhancing the process of their disruption and thereby liberating thrombokinase."

A recent and as yet unpublished report by Geoffrey Edsall[13] (Dept. of Pediatrics, Harvard Medical School and Children's and Infants' Hospitals, Boston), describes extensive *in vitro* experiments with *Daboia* venom, plasma, and various thromboplastic substances, including human placental coagulant, bovine brain extract, fresh purified cephalin, cow platelets, fibrinogen, prothrombin, and calcium ions. It is stated that the results of the experiments fit without any exception the general suggestion of Houssay and Sordelli, that the venom facilitates the action of thromboplastin. The detail of such an action remains a matter of speculation.

No thrombic action could be detected with concentrations of the venom up to 1:7,000 in solutions containing fibrinogen or citrated plasma. It would appear that (contrary to Ganguly's belief) the platelets are not specifically acted on by Russell viper venom since it will accelerate the coagulation of recalcified Berkefeld-filtered plasma. Thus the platelets cannot be regarded as essential to the coagulant action of the venom.

Edsall also demonstrated that the coagulant effect of the venom is not identical with that of thromboplastin since the two types of coagulant act synergistically in combination and the venom is also capable of reactivating to a large extent thromboplastic substances partially inactivated by heat, aging, or chemical treatment.

The *coagulative potency* of seventeen commercially available products for hastening the process of blood coagulation was biologically assayed by Aggeler and Lucia.[30] The materials examined included two varieties of snake venom, five thromboplastin solutions for local or oral administration, five thromboplastin solutions for hypodermic use, one tissue fibrinogen solution for oral use, one tissue fibrinogen solution for hypodermic use, one substance derived from bovine blood for oral, local or hypodermic use, and two types of refined horse serum for hypodermic use. The two venoms studied were the fer-de-lance (*Bothrops atrox*) and *Russell viper* (*Vipera russellii*).

The ranges of coagulation time for the saline-controlled specimens with which the various blood coagulating substances were compared were:

For *normal plasma*: 90–120 sec.

For *hemophilic plasma*: 400–500 sec.

1. Five preparations of thromboplastin solution for local or oral use coagulated normal plasma in from thirty-two to fifty-two seconds. The shortest coagulation times for these preparations with hemophilic plasma varied between forty-one and ninety seconds.

2. Two preparations of tissue fibrinogen for oral and hypodermic use, respectively, were inactive in every concentration in normal plasma and showed only slight potency in higher concentrations in hemophilic plasma.

3. Four preparations of thromboplastin solution for hypo-

dermic administration were found to be inactive in normal plasma. Of these, three were also inactive in hemophilic plasma. One preparation produced coagulation in fifty-four seconds in the ¼ and ⅛ dilutions in normal plasma and achieved the same results in sixty-four seconds in hemophilic plasma.

4. A preparation of bovine blood derivative for local, oral or hypodermic administration was inactive in any concentration in both normal and hemophilic plasma.

5. Two horse sera preparations were inactive in normal plasma and, of these, one was slightly coagulant when used in high concentrations in hemophilic plasma (C.T. 154 sec.).

6. Local solutions of thromboplastin derived from the brains of the horse, dog, calf, rabbit, sheep and guinea-pig, respectively, exhibited coagulation times in normal plasma of 24, 25, 34, 37, 90, and 113 seconds. In hemophilic plasma, the shortest coagulation times were, respectively, 26, 29, 41, 36, 135, and 395 seconds.

7. Hypodermic thromboplastin solutions derived from brains of the horse, dog, rabbit, sheep and guinea-pig were uniformly inactive in both normal and hemophilic plasma.

8. Fer-de-lance venom, dispensed commercially as a 1:5,000 solution, was found to produce a minimum coagulation time of forty-seven seconds in the ¼ dilution in normal plasma. The coagulation time in hemophilic plasma was fifty-seven seconds when the product was used in full strength. The commercial diluent in full strength was found to be slightly anticoagulant. A 1:5,000 solution of the venom in 0.85 per cent NaCl in full strength gave a coagulation time of twelve seconds in either hemophilic or normal plasma.

9. Dried Russell viper venom was readily soluble both in the commercial diluent and in 0.85 per cent NaCl. Parallel tests with either diluent gave almost identical results. When the product was used in full strength (1:10,000) the coagulation time was thirty seconds in both normal and hemophilic plasma, and in both instances the range of concentrations producing activity was broad.

The authors note that of the seventeen commercially available products, nine were found to be practically inactive. The only products found to be significantly active were those suit-

able for local or oral use and, of these, the two snake venom preparations possessed a degree of coagulative activity roughly comparable to that of the solutions of thromboplastin for local use.

Chemical Composition.—Ganguly and Melkana[14] have analyzed Russell viper venom chemically and report that it contains carbon, hydrogen, nitrogen, sulfur, and oxygen. There is no phosphorus, and consequently no substances such as lecithin, kephalin, and nucleoproteins. The dried venom contains 15.5 per cent protein nitrogen, indicating 96.8 per cent protein, and ether-soluble lipoids are present to the extent of 2.8 per cent. Of the protein present in Russell viper venom, 23.35 per cent is globulin, 22.12 per cent albumin, and 50.52 per cent proteoses. The neurotoxic, coagulant and hemorrhagic actions are thought to be due to secondary proteoses. By local application in 1:10,000 solution the venom appears to exert only its coagulant effect.

Clinical Use.—The first report of the hemostatic possibilities of Russell viper venom was made by Macfarlane and Barnett in 1934.[8]   In all the cases described complete hemostasis was secured almost immediately by the local application of sterile 1:10,000 solutions of the venom. In no case was any ill effect attributable to its use. The venom was used successfully some twenty times as a hemostatic application following *dental extraction* and *tonsillectomy* in patients with normal blood and in two cases during abdominal operations to control capillary oozing. The hemostatic solution was also used to stop hemorrhage following dental extraction in three subjects with hemorrhagic diathesis, of which no definite diagnosis was made. Finally, the authors state that in genuine hemophilic subjects, the Russell viper venom was most effectively employed following dental extractions (two cases), to control epistaxis (one case), and to control traumatic hemorrhage (one case).

A detailed account of the treatment of accessible hemophilic hemorrhage with Russell viper venom is given by the same authors in the St. Bartholomew's Hospital Reports.[15] The authors point out that during the summer of 1934, a research into the action of certain snake venoms on the coagulation of hemophilic blood was undertaken by the Pathological Depart-

ment of St. Bartholomew's Hospital with the cooperation of the Zoological Society of London.[16]   Table 1 gives a summary of the results obtained.

Various systems of treatment are discussed and nine cases exhibiting hemorrhagic diathesis are reviewed. Of these, seven received Russell viper venom. Dental extractions were carried

TABLE 1

COAGULANT EFFECT OF SNAKE VENOMS ON HEMOPHILIC BLOOD

Venom.	Coagulation time of blood + 1 : 10,000 venom.	Coagulation time of blood from same subject without venom.
Colubridae:		
Bungarus candidus........	4 minutes 25 seconds.	22 minutes 25 seconds.
Naja melanoleuca..........	No clot after 90 min.	35 minutes.
N. nigricollis.............	No clot after 90 min.	35 minutes.
N. naja....................	No clot after 90 min.	35 minutes.
N. naja (black var.)... ...	No clot after 90 min.	35 minutes.
N. hannah............... .	No clot after 90 min.	35 minutes.
Micrurus tschudii...... ...	No clot after 12 hours.	33 minutes.
Dendraspis angusticeps (black var.).............	28 minutes.	35 minutes.
Viperidae:		
Vipera ursinii.............	1 minute 33 seconds.	33 minutes.
V. berus.................	2 minutes 15 seconds.	22 minutes 25 seconds.
V. ammodytes.............	9 minutes 6 seconds.	35 minutes.
→*V. russellii*	17 seconds.	35 minutes.
Bitis arietans.............	45 minutes.	22 minutes 25 seconds.
B. nasicornis.............	5 minutes 22 seconds.	22 minutes 25 seconds.
Cerastes cerastes...........	38 seconds.	22 minutes 25 seconds.
Crotalidae:		
Agkistrodon piscivorus......	No clot after 12 hours.	33 minutes.
A. mokasen...............	No clot after 12 hours.	33 minutes.
Trimersurus purpureomacu-latus.................	1 minute 20 seconds.	22 minutes 25 seconds.
Crotalus confluentus.......	2 minutes 47 seconds.	33 minutes.
C. oreganus.............	7 minutes 42 seconds.	22 minutes 25 seconds.
C. horridus...............	12 minutes 28 seconds.	33 minutes.
C. pricei................	8 minutes.	35 minutes.

out in four cases and external wounds were treated in two. Russell's viper venom was used and transfusions were not required. Two cases required blood transfusions, one because of the mechanical difficulties encountered and the other because of gross infection, these factors leading to uncontrollable bleeding.

The work of Macfarlane and Barnett is discussed in the Lancet[17] as follows: "Fortunately the coagulant power of the venom does not diminish in direct proportion to the dilution and a coagulant effect could still be demonstrated after a dilution of $1:10^{18}$; thus, in high dilution, an extremely potent coagulant action is retained while other possible toxic effects of venom are absent. . . . Experience with other haemostatics has shown that Russell's viper venom is the most effective one available, and that if it fails others are not likely to succeed."

Chopra and Chowhan[18] state that the venom of the Russell viper is by far the most powerfully coagulant of all Indian snake venoms and that "in the case of haemophilia it was noticed that once the coagulation started with this venom the process of fibrin formation was completed rapidly. The clot produced was tough and elastic, in marked contradistinction to the soft slowly-forming ineffective clot characteristic of the hemorrhagic diathesis."

The first use of Russell viper venom in a *clinical emergency* is described by Baker and Gibson[19]: An eleven-year-old hemophilic boy was slowly becoming exsanguinated by a small but persistent hemorrhage from the gum around an upper incisor tooth. The venom was quickly supplied from the experimental stock at the Wellcome Physiological Research Laboratories and was administered the same day. Bleeding stopped at all three points and did not recur to any serious extent.

Barratt[20] submits the case report of a female patient, eighty years old, with a history of epigastric pain and occasional vomiting and a systolic blood pressure of 275 mm. of Hg. Hematemesis of several pints was treated with morphine and bed rest. When the condition did not improve and the pulse rate rose to 120, about 5 cc. of a 1:10,000 aqueous solution of Russell viper venom was administered by mouth. Vomiting of blood had continued to within half an hour of administration, that is for twenty-four hours. There was no further hematemesis. Recovery was uneventful. Barratt states, "It appears fairly clear that the condition was one of erosion of a blood vessel in an old ulcer crater. The high blood pressure compensated in some measure for the loss of blood volume, and probably contributed to the recovery of the patient; although it was also doubtless responsible for a greater degree of haem-

orrhage, if this was of arterial origin, as was probably the case. Apparently there is no danger from absorption of the venom at the site of the ulcer—at least in the dosage used."

Barnett and Macfarlane[21] commented upon the above report as follows: "It is safe to say that Russell's viper venom could safely be given in larger quantities than that represented by a single phial of stypven.* A 5 c.cm. phial of stypven contains 0.5 mg. of Russell's viper venom, and Acton and Knowles (postulating a susceptibility in man equal to that of monkeys) estimated the smallest fatal dose for man at 42 mg. Further, since snake venoms lose their toxicity before they are absorbed by the intestinal mucous membrane, only that proportion of the dose that comes in contact with the broken surface need be considered.

"We would suggest 5 c.cm. or 10 c.cm. of stypven or its equivalent, repeated if necessary, as a dose more certain to carry the coagulating enzyme to the bleeding surface. Since one would expect it to lose its activity fairly rapidly in the stomach, we think it would be reasonable to repeat the dose if the ulcer continued to bleed after half an hour."

The use of Russell viper venom for the *control of hemorrhage following tonsillectomy* is described by Hance[22]: A 48-year-old male Anglo-Indian, with a bleeding time of six minutes in spite of preparatory calcium-hemoplastin medication, underwent tonsillectomy with ensuing hemorrhage of the oozing variety: "Since neither continued pressure nor suture of the pillars succeeded in stopping this bleeding, small pledgets of sterile cotton-wool were soaked in 1:10,000 solution of Russell viper venom and these were swabbed over the tonsillar site. The effect was immediate and dramatic. The bleeding stopped forthwith, and the pillars of the fauces were sutured without trouble over a dry tonsillar bed."

The successful use of Russell viper venom by local application in the treatment of *epistaxis* was described by Higgins and Thorne[23]: The hemorrhage resisted all other treatment for six days. There was a history of hemophilia in the patient's brother and the patient himself had experienced severe hemorrhage after extraction of teeth. The venom solution was ap-

* "Stypven" Russell viper venom (not for injection); 0.1 mg. in 1 cc. and 0.5 mg. in 5 cc., issued by Burroughs-Wellcome & Co., New York.

plied by means of pledgets plugged into the nares and bleeding stopped at once.

The *risk* associated with the use of a powerful blood coagulant by injection is obvious. Nevertheless, there are at least two reports of the administration of Russell viper venom by this route. In one,[22] the author emphasizes that although the preparation used was labelled "most definitely . . . 'Not for injection,'" the desperate condition of the patient warranted the administration of the venom intravenously. Accordingly 0.5 cc. of a 1:100,000 aqueous solution was injected into the vein. This was repeated in ten minutes and later a blood transfusion was given. There was no further evidence of hemorrhage and the patient's condition progressively improved. In another case, half an hour before an operation for the removal of a gallbladder, 0.5 cc. of a 1:100,000 solution of Russell viper venom was injected intradermally. A second intradermal injection was given later and, following this, all visible oozing of blood completely stopped and did not recur.

The use of Russell viper venom by *injection* is described by Raimondi and Sangiovanni,[24] and an abstract of the report appears in the Year Book of General Therapeutics, 1937. It is there stated that the authors recommend use of the venom "in doses of 0.5 mg. (dissolved in 1 cc. of physiologic saline solution with 0.1 per cent tricresol) as an emergency remedy and advise that administration be repeated every four hours as required. In simple hemoptysis, this treatment suffices, but in the severe forms they advise first the injection of the venom solution, followed in four hours by 10 cc. of a 10 per cent solution of $CaCl_2$ or Ca Gluconate." This dosage would seem *excessive* and *extremely dangerous,* inasmuch as Russell viper venom is commercially available for local application only and in a strength of 1:10,000 rather than 1:2,000.

Mode of Administration.—Sterile, dried, standardized Russell viper venom is available in rubber-stoppered vials accompanied by ampules containing sufficient sterile, distilled water (with 0.5 per cent phenol) to make a 1:10,000 solution of the venom. With aseptic precautions, the solvent is added to the venom by means of a syringe and the solution is ready for use.

Russell viper venom in the dry state is stable if reasonable

precautions with regard to avoiding exposure to heat and strong sunlight are observed. Solutions of the venom, however, tend to lose their potency, and it is recommended that solutions be discarded after one week.

Russell viper venom is intended for *local* application and is generally administered by means of pledgets soaked in the solution. The venom should be applied directly to the point of bleeding; all intervening clots or other obstructions must be cleared away. It has been found advantageous in certain cases to pack the bleeding area with venom-impregnated pledgets and to leave them in place for several hours. Occasionally the clot is disrupted by the removal of the pledget and fresh bleeding ensues. This may be avoided by interposing a patch of sterile (oil-free) silk between the pledget and the tissue. In this way the fibrin clot does not become involved with the fibers of the gauze or cotton.

The venom may also be dropped directly onto the hemorrhagic area from the point of a small-caliber hypodermic needle.

In nasopharyngeal operations, solutions of the venom may be applied with convenience by means of an atomizer; this means of application is also effective in controlling the oozing type of hemorrhage so frequently seen in cervical carcinoma and other neoplasms to which local applications can be made.

Discussion.—Mellanby's revisions[25] of Howell's theory of the coagulation of the blood suggest the scheme[26] on page 787.

The investigations of Edsall[13] indicate that Russell viper venom facilitates the action of thrombokinase (thromboplastin); that it acts synergistically with thromboplastic substances, and is capable of reactivating to a large extent such factors partially inactivated by heat, aging, or chemical treatment.

But thrombokinase acts on prothrombase (prothrombin). The latter is partially or totally lacking in the blood of patients suffering from *obstructive jaundice*. Therefore it is reasonable to suppose that Russell viper venom would be ineffective in such cases, which are properly treated orally with bile salts and vitamin K[27] or with phthiocol[28] or quinones[29] having vitamin K activity.

Prothrombase (Prothrombin)

```
Thrombokinase + Ca++
(Thrombokinase alone acts very slowly)
```

Thrombase (Thrombin)

```
Heparin absent or
in small amounts.
```

Coagulation
(Fibrinogen converted
to fibrin)

```
Heparin and neutral salts present,
thrombase neutralized. Heparin is
derived from tissues (liver, etc.). An
antithrombase other than heparin
present in circulating blood.
```

No Coagulation

```
Addition of thrombokinase in ade-
quate amount annuls action of
heparin. Ca++ exerts no influence
upon this reaction.
```

Coagulation
(Fibrinogen converted into Fibrin)

With the exception of prothrombin-deficiency states, the local application of Russell viper venom should prove highly effective in the control of hemorrhage, particularly in cases of *hemophilia*.

No danger or undesirable side effects have been reported in connection with the proper administration of Russell viper venom, and it is our opinion that this substance constitutes a convenient and reliable hemostatic for local application.

Summary.—1. A review and discussion of the experimental and clinical evidence of the coagulant action of Russell viper venom is presented.

2. The venom appears to accelerate greatly the action of thromboplastic substances with which it acts synergistically.

3. Russell viper venom appears to be capable of reactivating thromboplastic substances partially inactivated by heat, aging, or chemical treatment.

4. Hemorrhage, with the probable exception of that associated with prothrombin deficiency, may be effectively and promptly controlled by the local application of aqueous (1:10,000) solutions of Russell viper venom.

5. In hemophilic patients, it has been observed that the clot rapidly produced by Russell viper venom is tough and elastic, in marked contradistinction to the soft, slowly-forming clot characteristic of the hemorrhagic diathesis.

6. Solutions of the venom are applied locally to the point of bleeding by means of pledgets, or directly by drops from a small-caliber hypodermic needle, or by means of an atomizer.

7. Local application of Russell viper venom solutions is indicated for the control of epistaxis, and hemorrhage associated with peptic ulceration, tonsillectomy, prostatic resection, plastic surgery, etc., and bleeding from any body surface that does not respond to the ordinary methods of hemostasis (pressure, etc.).

8. No harmful or undesirable effects have been reported in connection with the proper administration of the venom.

BIBLIOGRAPHY

1. Lamb, G., and Hanna, W.: Scientific Memoirs by Officers of the Medical and Sanitary Department of the Government of India (New Series), No. 3, 1903.

2. Lamb, G., and Hanna, W.: Scientific Memoirs by Officers of the Medical and Sanitary Department of the Government of India (New Series), No. 4, 1903.

3. Wooldridge: Proc. Roy. Soc., 1886.

4. Martin, C. J.: J. Physiol., 15: 380, 1894.

5. Arthus, M.: Arch. Int. de Physiol., 15: 203, 1920.

6. Houssay, B. A., and Sordelli, A.: J. de Physiol. et Path. Generale, 18: 781, 1921.

7. Brazil, V., and Vellard, J.: Ann. Inst. Past., 42: 402, 1928.

8. Macfarlane, R. G., and Barnett, B.: Lancet, 2: 985, 1934.

9. Taylor, G., Mallick, S. M. K., and Ahuja, M. L.: Ind. Jour. Med. Res., 23: 131, 1935.

10. Ganguly, S. N.: Ind. Jour. Med. Res., 24: 525, 1936.

11. Eagle, H.: J. Exp. Med., 65: 613, 1937.

12. Noc, F.: Ann. Inst. Past., 18: 387, 1904.

13. Edsall, G.: Unpublished report.

14. Ganguly, S. N., and Melkana, M. T.: Ind. J. Med. Res., 23: 997, 1936.

15. Macfarlane, R. G., and Barnett, B.: St. Bartholomew's Hospital Reports, 68: 229, 1935.

16. Barnett, B., and Macfarlane, R. G.: Proc. Zoological Soc., Part 4, p. 241, 1934.

17. Macfarlane, R. G., and Barnett, B.: Lancet, 2: 893, 1935.

18. Chopra, R. N., and Chowhan, J. S.: Ind. Med. Gaz., 70: 445, 1935.

19. Baker, G. A., and Gibson, P. C.: Lancet, 1: 428, 1936.

20. Barratt, A.: Brit. M. J., 2: 1083, 1936.

21. Barnett, B., and Macfarlane, R. G.: Brit. M. J., 2: 1286, 1936.

22. Hance, J. B.: Indian Med. Gaz., 72: 76, 1937.

23. Higgins, L., and Thorne, R. T.: Brit. M. J., 1: 640, 1936.

24. Raimondi, A. A., and Sangiovanni, A.: Prensa med. argent., 24: 42, 1937.

25. Mellanby, J.: Proc. Roy. Soc., 107: 271, 1930; 113: 93, 1933; 116: 1, 1934.

26. Best, C. H., and Taylor, N. B.: "Physiological Basis of Medical Practice," p. 143, Wm. Wood & Co., 1937.

27. Butt, H. R., Snell, A. M., and Osterberg, A. E.: J.A.M.A., 113: 383, 1939.

28. Fernholz, E., and Ansbacher, S.: Science, 90: 215, 1939.

29. Fieser, L. F., Bowen, D. M., Campbell, W. P., Fieser, M., Fry, E. M., Jones, R. N., Riegel, B., Schweitzer, C. E., and Smith, P. G.: J.A.C.S., 61: 1925, 1939.

30. Aggeler, P. M., and Lucia, S. P.: Am. J. Med. Sci., 199: 181, 1940.

CLINIC OF DR. THOMAS H. McGAVACK

DEPARTMENT OF MEDICINE AND MEDICAL SERVICE, NEW YORK
MEDICAL COLLEGE AND FLOWER AND FIFTH AVENUE HOS-
PITALS

SOME RECENT ADVANCES IN THE TREATMENT OF HEMOPHILIA

THE difficulties encountered in the treatment of hemophilia depend upon the hereditary nature of the disease, and our imperfect knowledge of the clotting process in both normal and hemophiliac individuals. Therapy directed to the underlying hereditary defect is entirely prophylactic and its success will be directly proportional to our ability to prevent intermarriage in hemophiliac families, and to legalize the sterilization or abortion of all potential transmitters.

The foundations for the development of measures effective in controlling the hemorrhagic incidents in the life of the hemophiliac must be laid in a better understanding of blood coagulation as it occurs in both the normal and the affected subject. The clotting process appears to be a biphasic reaction, concerned respectively with the formation of thrombin (thrombase) and fibrin. It may be best conceived as enzymic in character[1] and capable of expression in the following qualitative formulae:

Reaction I.—Prothrombin (prothrombase) + (calcium) + "thromboplastic substance" (thromboplastins) = thrombase (thrombin).

Reaction II.—Thrombase + fibrinogen = fibrin.

In the formation of thrombase (Reaction I), prothrombin (thrombogen) (prothrombase) (proserozyme) is the quantitatively used plasma factor, which can be converted in a variety of ways into thrombase. In fact Mellanby[2] believes

that this conversion may take place spontaneously in the absence of thromboplastic substance (thromboplastin) (thrombokinase) (cytozyme), or calcium, or both, but at a very much diminished rate, although this is questioned by other observers.[3]

Under normal conditions, it is generally conceded that, while calcium and thromboplastic substance are both necessary for the rapid completion of clotting, very little of either is used. The enzymic or catalytic character of the reaction is suggested. Moreover, the fact that trypsin, certain snake venoms (e.g. *Bothrops atrox;* Russell's viper; and *Notechis scutatus*) and other proteolytic enzymes can act upon prothrombin to mimic the reaction is still further indication of the enzymic nature of the thrombokinase-calcium system.

In the past, it has been generally believed that only in its diffusible ionic form is calcium effective in clotting blood. The recent work of Ferguson[4] favors the view that ionization from non-diffusible combinations may occur at colloidal surfaces, and that both diffusible and non-diffusible calcium are therefore available in completing Reaction I.

While our enzymic view of the clotting process would have favored the use of the term "thrombokinase" rather than that of "thromboplastic substance," the latter seems more generic and not open to the possible criticism that it refers alone to the aqueous tissue extracts used by Morawitz[5] and later observers. Under the term we should recognize aqueous, saline, and alcoholic extracts of tissues, platelets, and certain blood plasma fractions which possess a common ability to change prothrombin to thrombase rapidly in the presence of calcium and slowly in its absence.

When the influence of inhibiting substances is removed, thrombase quickly changes available fibrinogen to fibrin, thus completing Reaction II of clot formation.

It has been well established that the *clotting defect* in hemophilia is concerned with the conversion of prothrombin to thrombase, *i.e.*, with Reaction I. While prothrombin values are normal, and a normal calcium level and partition exist, it has been shown recently by a number of workers[6, 7, 8, 9, 10, 11, 12] that a thromboplastic substance is lacking. The platelets are a recognized source of such material, and for some years it was believed that the reason for prolonged coagulation time in

hemophilia was a retardation in platelet disintegration.[13] The subsequent work of Howell[13] and of Lee and Erickson[14] suggests that platelets, while present in usual numbers, disintegrate more slowly than normally in the shed blood of the hemophiliac, not because of inherent defect, but because of something lacking in the blood plasma. Likewise Patek and Stetson[7] have demonstrated that the platelets of hemophiliac blood behave entirely similarly to platelets from other sources. Moreover, they have isolated a coagulation-promoting substance (thromboplastic substance) ("globulin substance") from the plasma of normal individuals which has been shown to be diminished in the blood of the hemophiliac. Subsequent communications of these workers and their associates[7, 8, 9, 10, 11, 15, 16] have confirmed the earlier experience, and a more refined preparation, "euglobulin substance" has been developed. Their work has been repeatedly confirmed,[6, 12, 17] and the globulin substance has been shown to be similar to, if not identical with, the thromboplastic material which has been isolated from nearly every tissue of the body and found in particularly high concentrations in the brain and lung (the thrombokinase of Morawitz).[5] Howell[13] comments at length on the properties of this material and concludes that, in its purest form, it is both protein and carbohydrate free, gives positive reactions for phosphorus and nitrogen, and probably contains a glycerophosphate group. He finds it adsorbed to the globulins of the blood plasma and to the nucleoproteins of the lung, and in each instance precipitated with the corresponding protein. "Globulin substance" would seem therefore to be a misnomer. The terms, "plasma thromboplastin" and "tissue thromboplastin," suggested by Howell,[13] are preferable and will be used in further discussion unless a particular preparation is to be designated.

Our method of therapeutic approach to the underlying problem in hemophilia is predicated upon the apparently well proven conceptions that a deficiency exists in both plasma and tissue thromboplastins, and that the behavior of these substances is similar to that of certain proteolytic enzymes. The following agents deserve consideration:

I. Thromboplastins.—Numerous attempts have been made to market tissue extracts for the control of hemophilia

that this conversion may take place spontaneously in the absence of thromboplastic substance (thromboplastin) (thrombokinase) (cytozyme), or calcium, or both, but at a very much diminished rate, although this is questioned by other observers.[3]

Under normal conditions, it is generally conceded that, while calcium and thromboplastic substance are both necessary for the rapid completion of clotting, very little of either is used. The enzymic or catalytic character of the reaction is suggested. Moreover, the fact that trypsin, certain snake venoms (e.g. *Bothrops atrox;* Russell's viper; and *Notechis scutatus*) and other proteolytic enzymes can act upon prothrombin to mimic the reaction is still further indication of the enzymic nature of the thrombokinase-calcium system.

In the past, it has been generally believed that only in its diffusible ionic form is calcium effective in clotting blood. The recent work of Ferguson[4] favors the view that ionization from non-diffusible combinations may occur at colloidal surfaces, and that both diffusible and non-diffusible calcium are therefore available in completing Reaction I.

While our enzymic view of the clotting process would have favored the use of the term "thrombokinase" rather than that of "thromboplastic substance," the latter seems more generic and not open to the possible criticism that it refers alone to the aqueous tissue extracts used by Morawitz[5] and later observers. Under the term we should recognize aqueous, saline, and alcoholic extracts of tissues, platelets, and certain blood plasma fractions which possess a common ability to change prothrombin to thrombase rapidly in the presence of calcium and slowly in its absence.

When the influence of inhibiting substances is removed, thrombase quickly changes available fibrinogen to fibrin, thus completing Reaction II of clot formation.

It has been well established that the *clotting defect* in hemophilia is concerned with the conversion of prothrombin to thrombase, *i.e.*, with Reaction I. While prothrombin values are normal, and a normal calcium level and partition exist, it has been shown recently by a number of workers[6, 7, 8, 9, 10, 11, 12] that a thromboplastic substance is lacking. The platelets are a recognized source of such material, and for some years it was believed that the reason for prolonged coagulation time in

hemophilia was a retardation in platelet disintegration.[13]   The subsequent work of Howell[13] and of Lee and Erickson[14] suggests that platelets, while present in usual numbers, disintegrate more slowly than normally in the shed blood of the hemophiliac, not because of inherent defect, but because of something lacking in the blood plasma.   Likewise Patek and Stetson[7] have demonstrated that the platelets of hemophiliac blood behave entirely similarly to platelets from other sources. Moreover, they have isolated a coagulation-promoting substance (thromboplastic substance) ("globulin substance") from the plasma of normal individuals which has been shown to be diminished in the blood of the hemophiliac.   Subsequent communications of these workers and their associates[7, 8, 9, 10, 11, 15, 16] have confirmed the earlier experience, and a more refined preparation, "euglobulin substance" has been developed. Their work has been repeatedly confirmed,[6, 12, 17] and the globulin substance has been shown to be similar to, if not identical with, the thromboplastic material which has been isolated from nearly every tissue of the body and found in particularly high concentrations in the brain and lung (the thrombokinase of Morawitz).[5]   Howell[13] comments at length on the properties of this material and concludes that, in its purest form, it is both protein and carbohydrate free, gives positive reactions for phosphorus and nitrogen, and probably contains a glycerophosphate group.   He finds it adsorbed to the globulins of the blood plasma and to the nucleoproteins of the lung, and in each instance precipitated with the corresponding protein.   "Globulin substance" would seem therefore to be a misnomer.   The terms, "plasma thromboplastin" and "tissue thromboplastin," suggested by Howell,[13] are preferable and will be used in further discussion unless a particular preparation is to be designated.

Our method of therapeutic approach to the underlying problem in hemophilia is predicated upon the apparently well proven conceptions that a deficiency exists in both plasma and tissue thromboplastins, and that the behavior of these substances is similar to that of certain proteolytic enzymes.   The following agents deserve consideration:

I. Thromboplastins.—Numerous attempts have been made to market tissue extracts for the control of hemophilia

and other bleeding dyscrasias: *coagulen* (Ciba), *fibrogen* (Merrell), *thromboplastin* (Armour, Cutter, Lederle, Squibb), *clauden* (Kretschmar), *hemagulen* (Lilly), *hemostatic serum* (Parke Davis), and so forth. The therapeutic value of these agents must be carefully weighed as contradictory results have been obtained from their administration, and their potency often has been difficult to maintain over any very long period of time.

"GLOBULIN SUBSTANCE."—This material has been prepared from human or beef blood according to the method of

TABLE 1

ACCELERATING EFFECT OF VARIOUS SUBSTANCES ON CLOTTING TIME
Average Clotting Time in Minutes

Case No.	Number of tests.	Control.	Human plasma.	Human "globulin substance."	Fer-de-Lance venom. 1 : 5000	Russell's viper venom.	
						1 : 5000	1 : 10,000
Case 1..	2	20	2½	2½	3	1½	3
Case 2..	4	35	2	2	4	½	1
Case 3..	4	94	3	3	4	3½	4½
Case 4..	3	115	5	5	4	1½	2½
Case 5..	3	60	2	2	3	¼	½
Case 6..	2	80	2½	2½	3	½	¾

Two cc. of patient's blood used in each test. In the case of human plasma and "globulin substance" 0.03 cc. of the respective solutions added. Five drops fer-de-lance venom or Russell's viper venom used in the respective tests.

Patke and Stetson.[7] Between 250 and 300 mg. of dried globulin substance may be recovered from each 100 cc. of blood used. When diluted to the blood volume from which originally obtained, as little as 0.03 cc. will reduce the clotting time of 2 cc. of hemophiliac blood to well within normal limits (Table 1). Due to destruction in the stomach, it is ineffective when given by mouth. Because of the danger of serum reactions, beef globulin substance has only been applied for its local hemostatic effects.[11] When it is taken up in powder form on small packs of *dry* gauze and applied to the freshly cleaned bleeding surface, normal clot formation ensues. We have used

it successfully in hemophiliacs; on three occasions following tooth extractions, in the treatment of three superficial cuts, and in one case of repeated nosebleeds.

"Globulin substance" of human derivation may be used both intravenously and intramuscularly, the *dosage* varying from 50 to 300 mg. of the powdered substance (equivalent to from 20 to 100 cc. of blood) made up to the original volume of blood from which derived.   Figure 101 shows the effect of
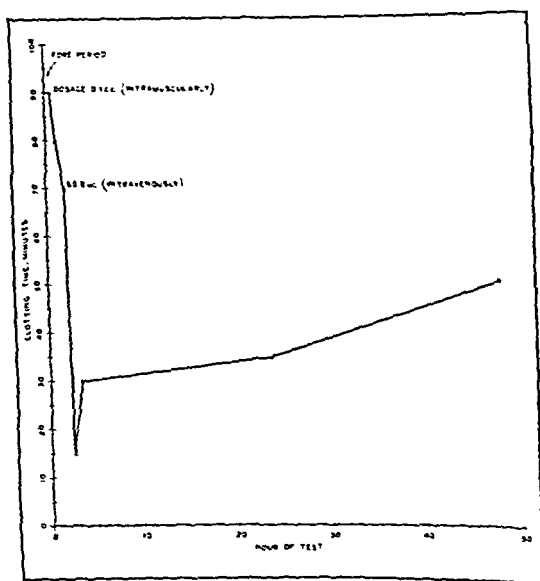
Fig. 101.—Effect of "globulin substance" *in vivo*. Human blood used.

200 mg. given intravenously. It will be noted that the greatest effect on clotting time occurs within the first four hours, and this gradually diminishes until the original level is reached in from twenty-four to forty-eight hours. Intramuscular administration in equivalent amounts shows a similar response.

Globulin substance is indicated in the control of acute bleeding episodes in the hemophiliac individual. Blood transfusions may answer the same purpose but necessitate the delays incident to procuring compatible donors and the ever present possibility of transfusion reaction.

Disadvantages.—1. The amount of human blood necessary

to success is large, and practically precludes any commercial preparation of this material.

2. Material so prepared maintains its potency for a limited period of time (Fig. 102).

3. Repeated injections over short periods of time are associated with a refractory state in which no response occurs or in which further administration results in an actual prolongation of the bleeding time. The nature of this refractory phase is not clear, but is thought by some observers[1, 6] to indicate the
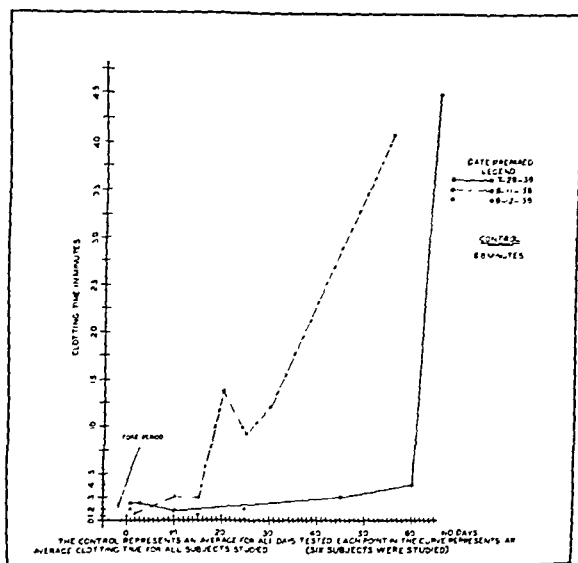
Fig. 102.—Rate of deterioration of "globulin substance." Human blood used.

enzyme-like activity of the thromboplastin as first suggested by Morawitz.[5]

EUGLOBULIN SUBSTANCE.—The clot promoting activities of this substance, isolated by Lozner and Taylor,[15] resemble those of "globulin substance."

However, it possesses several distinct *advantages:* Its preparations contain much less of foreign reagents. It shows a "maximum solubility in isotonic saline." On single injection, its lowering of clotting time is comparable to that of "globulin substance," whereas on repeated administration it is "capable

TABLE 2

EFFECTS OF TISSUE EXTRACTS IN VITRO

Type of tissue extract.	Clotting time.	
	Case 5.	Case 6.
Control..............................	60′	80′
Lung.........	1′	1′
Placental*...............	45″	45″
Liver........	1′	1′
Muscle..............	2′	1′45″
Kidney...........	2′	2′
Dilution 1 : 3		
Lung..........	1′30″	1′30″
Placental..	1′45″	1′45″
Liver.......................	1′45″	1′45″
Muscle...	2′	1′30″
Kidney.....	2′	2′
Dilution 1 : 5		
Lung.........	3′	3′
Placental.......	2′30″	2′30″
Liver.........	3′	3′
Muscle..	3′	3′
Kidney...	3′	3′
Dilution 1 : 10		
Lung..........	3′	3′
Placental........	2′30″	2′30″
Liver.....	3′	3′
Muscle.......	3′30″	3′30″
Kidney.....	3′30″	3′30″

* Fresh human placentas were used.
Prepared according to method used by Eley-Greene-McKann.

of maintaining the coagulation time at the lowered level with no indication of a refractory period which develops after the injection of 'globulin substance.' " Lozner and Taylor[15] have been able to maintain consistently lowered clotting times in three patients over periods varying from one and one half to several days by the six hourly administration of "euglobulin substance," and have yet to encounter a refractory phase. This appears to be an important step forward in the practical application of the thromboplastins.

PLACENTAL EXTRACT.—Extracts of the human placenta prepared according to the method of Eley, Green and McKhann[18] (*tissue thromboplastin*) show *in vitro* (Table 2) and *in vivo* effects similar to those obtained from globulin substance (*plasma thromboplastin*). Each cubic centimeter of the finished aqueous solution represents the coagulation-promoting substances present in approximately 5 gm. of fresh tissue or placenta from which sex hormones have been previously removed by boric acid extraction.* There is no difference in the potency of the substances obtained in the two instances. This is obvious proof of the fact that the placental coagulating factor is in no way related chemically or pharmacologically to estrogenic or other female hormones.

Coagulation-promoting extracts of placental origin must be used only *by mouth*, as they have routinely produced intravascular clotting in small laboratory animals when given intravenously or intramuscularly.

Eley and his associates[18] have administered the placental preparations to nineteen children suffering with hemophilia. In twelve the clotting time was reduced to within normal limits, the reduction lasting from forty-eight to seventy-two hours. The dosages found useful have been extremely variable: In one instance the above workers were able to maintain normal clotting time and freedom from hemorrhage for a period of seven months by the administration of 5 cc. of the extract twice weekly; in a second case, for eight months with 5 cc. at three- to five-day intervals. We have obtained lowering of the clotting time to within normal limits with doses as small as 3 cc. and no appreciable effect upon coagulation with as much as

* This placental material has been supplied to us through the courtesy of Dr. Stanley Beard of the Lederle Company

10 cc. The coagulation lowering effect from a single dose has not lasted longer than twenty-four hours in our hands, and usually but from six to eight hours. The tendency to the development of a refractory state is marked; actual prolongation of clotting time is a cumulative effect difficult to avoid (Fig. 103).

Advantages.—1. The effectiveness of the drug by mouth.

2. The ready availability of large supplies of material.

Disadvantages.—1. The wide variation in effective dosage.

2. The cumulative effects, with reversal of action which is difficult to predict.

3. The tendency to intravascular clotting, which precludes parenteral use in time of emergency.
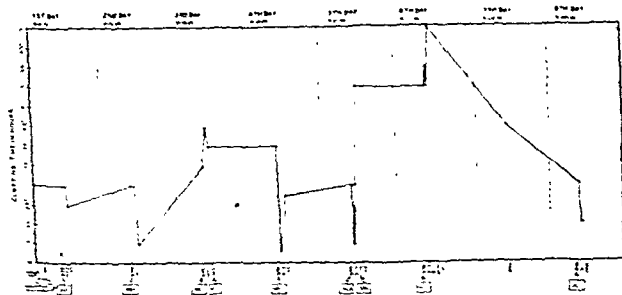
Fig. 103.—Cumulative effect of large doses of placental extract. (Case 5.)

OTHER TISSUE EXTRACTS.—Aqueous and saline extracts of other tissues, as aforesaid, contain coagulation-promoting substances which are believed to be identical with those obtained from the placenta.[13] The lung and brain have proven to be exceptionally rich in such material.[13, 17] Their action *in vitro* is shown in Table 2. These substances are precipitated from the tissues in conjunction with nucleoproteins, from which they can be, and have been, freed[13] in order to facilitate chemical investigation. Thromboplastin of tissue origin (usually beef brain) has been marketed by several firms for some time past, but its effectiveness in controlling the episodes of bleeding in the hemophiliac has not been satisfactorily demonstrated, possibly in part because of the small dosages used, and in part because of loss of active thromboplastic substances in the extraction process and upon standing.

The preparation of protein-free potent tissue extracts is the present important developmental step in the therapy of hemophilia.[18] It will enable the parenteral application of coagulation-promoting substances of animal origin, thus opening the way to a relatively inexpensive, readily available supply of effective material.

II. Proteolytic Enzymes.—While evidence has been accumulating for a number of years relative to the effect of proteolytic enzymes on the clotting of blood, Eagle[1] deserves credit for a critical comparison between such activity and the fundamental processes normally concerned in the coagulative activity.

He has shown that trypsin and certain snake venoms activate prothrombin in a manner similar to that of the normal calcium thromboplastin combination. Moreover, "if one follows the rate at which thrombin is elaborated from prothrombin under the influence of the calcium-platelet system, snake venoms, or crystalline trypsin, one obtains similar curves." These reactions show the reversibility common to all enzymic activity. Both blood and tissue thromboplastins have repeatedly produced a similar biphasic effect upon coagulation.[1, 3, 7, 18, 19]

Despite this increasing knowledge of the nature of blood clotting, the practical application of the proteolytic enzymes to the clinical problems of hemophilia has not met with a great deal of success.

SNAKE VENOMS.—Of the snake venoms, an ability to transform prothrombin to thrombase has been demonstrated for the Australian tiger snake (*Notechis scutatus*), the fer-de-lance (*Bothrops atrox*), the jararaca (*Bothrops jararaca*), and Russell's viper. Their effects upon the clotting of hemophiliac blood *in vitro* and *in vivo* are marked (Table 1).[1, 20, 21] We have found the venom of Russell's viper* slightly more active than that of the fer-de-lance, but both are capable of reducing the clotting time of hemophiliac blood to within normal limits when used in actual concentrations of 1:35,000 and 1:70,000 (Table 1). Eagle[1] found them to be effective in extraordinarily high dilution, often exceeding 1:1,000,000. Unlike Macfarlane,[20] we have obtained very little result in applying solu-

* We are obliged to Dr. Thos. Githens of the Sharpe and Dohme Laboratories for the venom preparations used in these studies.

tions of 1:10,000 strength directly upon open wounds or tooth sockets. Russell's viper venom in powdered form has been tried successfully in one case of hemophilia following tooth extraction. In this instance the effects were equal in every way to those obtained in other patients by the application of powdered "globulin substance" from beef plasma. While some use has been made of the snake venoms by *injection*,[22] it seems unlikely that they will gain wide favor except as local styptics, at least until local and systemic reactions to injection can be controlled and dosages so regulated as to give dependable, predictable effects upon the clotting time.

OTHER PROTEOLYTIC ENZYMES.—The snake venoms represent the only proteolytic enzymes which have been given clinical trial in hemophilia, but studies of the effects of *crystalline trypsin* on hemophiliac and normal bloods *in vitro* have been illuminating. They may later result in preparations capable of local and systemic application to disturbances in the clotting process.[1, 23] In hemophilia, *trypsin* and other proteases may make "free cephalin" available to promote the conversion of prothrombin to thrombin,[23] but the simple addition of cephalin has no effect unless sufficient enzyme is simultaneously present to prevent inert combinations of the former with the plasma proteins. Chargaff and Cohen[24] found "no activating effect on the clotting time" from the addition of "free cephalin."

III. **Miscellaneous Agents.**—Numerous agents have been tried from time to time in hemophilia, of which Howell[12] mentions a number only to emphasize their futility. These include *vitamins A, B, C, D; liver; cephalin; spleen* and *bonemarrow extracts; follicular hormones*,[25] *gonadotropic hormones*,[26] and so forth. On the other hand, such widely variant things as *egg white*,[27] *histidine*,[28] *liver*,[29] and *ovarian hormones*[30] have been reported to exert a favorable influence upon the clinical course of the disease. Most of the evidence showing the usefulness of any of the above-mentioned agents rests on purely clinical grounds. It is therefore difficult to evaluate, particularly in view of the wide fluctuations to be seen in the clotting time and the spontaneous exacerbations and remissions to which the hemophilac subject is prone.

BLOOD TRANSFUSION.—Blood transfusion has been the lifesaving therapeutic measure in hemophilia for many years.

Small transfusions[7, 31] of 40 to 50 cc. are satisfactory, providing the patient's loss of blood has not already been excessive.

DI-CARBOXYLIC ACIDS.—Recently, Brown and Steinberg,[32] in a search for an anticoagulant, have prepared an extract from shepherd's purse (*Thlaspi bursa pastoris*) which possesses clot-promoting properties, believed by them to be related to its content of di-carboxylic acids. Apparently the conversion of prothrombin to thrombin is hastened in some as yet undetermined way by the use of this agent.[32] Clinical studies on four patients with hemophilia are interesting.* The material used is obtainable in aqueous solution, is free of protein matter, and so standardized as to contain two clotting units† per cubic centimeter.

The shortening of the clotting time from a single 5 cc. dose of the drug intravenously administered lasts for about two to four hours. In treating bleeding episodes in hemophiliacs it has been our aim to maintain a lowered clotting time for several hours in order to ensure the normal formation of a good coagulus. On *admission,* therefore, a dose of 5 cc. has been administered intravenously, followed at three hourly intervals with a 2 cc. dose intramuscularly. Four hemophiliacs have been observed: one with hematuria; one with an abscessed tooth demanding extraction; one with epistaxis; and one with widespread knee, thigh and hip hemorrhage totally incapacitating him as a result of stiffness and pain.

In the first mentioned patient with hematuria, a boy eleven years old, the clotting time was never brought within normal limits, but was markedly reduced (from 125 minutes to 55 minutes). Moreover, the bleeding, which on admission accounted for one-fifteenth of the urinary volume, had completely stopped within twenty-eight hours, and red cells were absent from the urine at the end of thirty-six hours. This individual had had previous hematuria demanding several weeks of hospitalization and repeated transfusions.

The patient with the abscessed tooth, a male age twenty-

* We are indebted to the John A. Millar Company for the material (*Koagamin*) used in these studies

† A clotting unit is defined as the minimum amount of the material which, when injected intravenously into a 5 pound rabbit, will reduce the coagulation time by 50 per cent within fifteen minutes after administration.

four, is a very mild hemophiliac, who entered the hospital with a coagulation time of twenty-three minutes. This was reduced by his first dose of extract of shepherd's purse (*Koagamin*) to 2.5 minutes. It remained at approximately that level throughout his forty-eight hours in the hospital on sustaining doses of 2 cc. every four hours. His postoperative course was uneventful until the fifth day.

On three previous occasions he had had serious bleeding following extractions of an abscessed tooth, in each instance demanding at least one transfusion, and on one occasion almost resulting fatally. On the fifth day postoperatively, he returned to the hospital with some oozing from the socket; this was completely relieved by wiping out the clot and giving *Koagamin* according to the usual plan to a total dosage of 11 cc. Blood clotting time was reduced from twenty-one minutes to two minutes following the first injection made at that time.

The third patient, a boy thirteen years old, has throughout life suffered from epistaxis, recurring every several days and usually controlled with difficulty. He was admitted in a bleeding episode, which stopped shortly thereafter, and probably without reference to *Koagamin* therapy. His clotting time, however, showed prompt responses to 5 cc. doses of *Koagamin*, which in each instance were not sustained beyond two hours. Variations in clotting from an initial value of 360 minutes to a post-injection level of forty minutes were noted. In attempting to maintain a constant low level, with frequently repeated doses to a total of 24 cc. daily, an actual lengthening of the clotting time to 540 minutes was observed, though no active bleeding episode ensued.

In the fourth patient, a boy eight years old, the clotting time on admission was 160 minutes. This was reduced to thirty-five minutes following the first injection of *Koagamin* (5 cc. intravenously) and sustained at levels ranging from twenty-five to fifty-five minutes for three days with an average daily dose of 18 cc. administered intramuscularly.

While the action of this drug is not fully understood, it does seem from clinical trial that it may prove to be a useful agent in the management of the hemorrhages of the hemophiliac. If its ability to maintain lowered blood clotting levels is further confirmed, its advantages in the management of hemophilia

seem rather patent. It is a stable chemical compound of constant composition. It contains no protein and hence is free from the dangers of protein reactions of any sort. It is nontoxic, isotonic with the blood, and will not produce hemolysis. Its administration is simple, and the response prompt.

Conclusions.—Recent advances in the treatment of hemophilia are an outgrowth of an increasing knowledge of the clotting process in normal persons, and of the clotting defect to be seen in afflicted individuals.

Human *"euglobulin substances"* (plasma thromboplastin), *protein-free tissue extracts* (tissue thromboplastin), and *dicarboxylic acid compounds* at the present time seem to offer the most hopeful solutions to the problems involved in the management of the actively bleeding case.

BIBLIOGRAPHY

1. Eagle, H.: *Recent Advances in the Blood Coagulation Problem.* Medicine, 16: 95, 1937.

2. Mellanby, J.: Prothrombase, its Preparation and Properties. *Proc. Roy. Soc., S. B.,* 107: 271, 1930.

3. Ferguson, J. H., and Erickson, B. N.: The Coagulant Action of Crystalline Trypsin, Cephalin, and Lung Extracts. *Am. J. Physiol.,* 126: 661, 1939.

4. Ferguson, J. H., and Erickson, B. N.: The Rôle of Proteolytic Enzymes, Phospholipids, and Tissue Extracts in Blood Coagulation. (Soc. Proc.), *Am. J. Physiol.,* 126: 490, 1939.

5. Morawitz, P.: Beiträge zur Kenntnis der Blutgerinnung. *Beitr. z. chem. Phys. u. Path.,* 5: 133, 1904.

6. Bendien, W. M., and van Creveld, S.: Investigations on Hemophilia. *Am. J. Dis. Child.,* 54: 713, 1937.

7. Patek, A. J., Jr., and Stetson, R. P.: Hemophilia. I. The Abnormal Coagulation of the Blood and its Relation to the Blood Platelets. *J. Clin. Investigation,* 15: 531, 1936.

8 Patek, A. J., Jr., and Taylor, F. H. L.: Hemophilia. II. Some Properties of a Substance Obtained from Normal Human Plasma Effective in Accelerating the Coagulation of Hemophilic Blood. *J. Clin. Investigation,* 16: 113, 1937.

9. Pohle, F. J., and Taylor, F. H. L.: The Coagulation Defect in Hemophilia. The Effect in Hemophilia of Intramuscular Administration of a Globulin Substance Derived from Normal Human Plasma. *J. Clin. Investigation,* 16: 741, 1937.

10. Pohle, F. J., and Taylor, F. H. L.: The Coagulation Defect in Hemophilia. The Use of a Globulin Substance Derived from Beef Plasma as a Local Hemostatic in Hemophilia. *J Clin. Investigation,* 17: 501, 1938.

11. Pohle, F. J., and Taylor, F. H. L.: The Use of a Globulin Substance Derived from Beef Plasma as a Local Hemostatic in Hemophilia. *J. Clin. Investigation,* 17: 677, 1938.

12. Howell, W. H.: Hemophilia. Bull. New York Acad. Med., **15**: 3, 1939.

13. Howell, W. H., and Cekada, E. B.: The Cause of the Delayed Clotting of Hemophilic Blood. Am. J. Physiol., **78**: 500, 1926.

14. Lee, P., and Erickson, B. N.: Platelet Studies in Normal Men and Women (Menstruating and Non-Menstruating) and Subjects with Bleeding Disorders; Counts, Disintegration Rates, and Intradermal Platelet Injections. J. Lab. and Clin. Med., **24**: 821, 1939.

15. Lozner, E. L., and Taylor, F. H. L.: The Coagulation Defect in Hemophilia; Studies of the Clot Promoting Activity Associated with Plasma Euglobulin in Hemophilia. J. Clin. Investigation, **18**: 821, 1939.

16. Lozner, E. L., Kark, R., and Taylor, F. H. L.: The Coagulation Defect in Hemophilia: the Clot Promoting Activity in Hemophilia of Berkefelded Normal Human Plasma Free from Fibrinogen and Prothrombin. J. Clin. Investigation, **18**: 603, 1939.

17. Dam, H., and Glavind, J.: The Clotting Power of Human and Mammalian Blood in Relation to Vitamin K. Acta med. Scandinav., **96**: 108, 1938.

18. Eley, R. C., Green, A. A., and McKhann, C. F.: The Use of a Blood Coagulant Extract from the Human Placenta in the Treatment of Hemophilia. J. Pediat., **8**: 135, 1936.

19. Eley, R. C.: Hemophilia. M. Clin. North America, **21**: 375, 1937.

20. Macfarlane, R. G.: The Treatment of Hemophilic Haemorrhage. St. Barth. Hosp. Rep., **68**: 229, 1935.

21. Macfarlane, R. G., and Barnett, B.: The Haemostatic Possibilities of Snake-Venom. Lancet, **2**: 985, 1934.

22. Peck, S. M.: Attempts at Treatment of Hemorrhagic Diathesis by Injections of Snake Venom. Proc. Soc. Exper. Biol. and Med., **29**: 579, 1932.

23. Ferguson, J. H.: The Clotting of Hemophilic Plasma by Thromboplastic Enzyme. Am. J. Physiol., **126**: 669, 1939.

24. Chargaff, E., and Cohen, S. S.: On Lysophosphatides. J. Biol. Chem., **129**: 619, 1939.

25. Stetson, R. P., Forkner, C. E., Chew, W. B., and Rich, M. L.: Negative Effect of Prolonged Administration of Ovarian Substances in Hemophilia. J.A.M.A., **102**: 1122, 1934.

26. Chew, W. B., Stetson, R. P., Smith, G., and Smith, O.: Estrogenic, Luteal and Gonadotropic Hormones in Hemophilia. Arch. Int. Med., **55**: 431, 1935.

27. Timberley, W. A., Naish, A. E., and Clark, G. A.: A New Method of Treatment in Haemophilia. Lancet, **2**: 1142, 1936.

28. Kohl, H.: Histidinbehandlung der Hämophilie. Ztschr. f. klin. Med., **132**: 40, 1937.

29. Pickering, J. W.: Recognition, Treatment and Aetiology of Haemophilia. Lancet, **1**: 1239, 1929.

30. Birch, C. L.: The Otolaryngological Manifestations of Hemophilia. Ann. Otol., Rhin. and Laryng., **47**: 540, 1938. (Soc. Proc.)

31. Feissly, R.: Études sur l'hémophilie. Bull. et mém. Soc. méd. d. hôp. de Paris, **47**: 1778, 1923.

32. Steinberg, A., and Brown, W. R.: A New Concept Regarding the Mechanism of Clotting and the Control of Hemorrhage. (Soc. Proc.) Am. J. Physiol., **126**: 638, 1939.

CLINIC OF DRS. A. A. WEECH, E. GOETTSCH, AND J. D. LYTTLE

DEPARTMENT OF PEDIATRICS, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY

INTRAVENOUS INJECTION OF SERUM AND ACACIA IN THE TREATMENT OF EDEMA

SYSTEMS of therapy rise and fall. Methods of treatment which in one decade were regarded as specific are relegated to dusty tomes by the advent of the next. For those who ponder the meaning of tides in therapeutic enthusiasm, nihilism can be avoided only by a willingness to search critically the data which accumulate during the flood in order that something will remain to carry over into the ebb.

For several years we have been assembling observations during the treatment of edema with injections of serum and acacia. Until experience has been amplified it is not possible to appraise finally the wisdom of these procedures. That they are not specific is clear; that they sometimes lead to gratifying diuresis is likewise apparent.[1] Our purpose at this time is merely to tell the result of a critical examination of findings so far recorded. These findings may assist in an understanding of the diuresis; they should prove useful in future attempts to apply these types of treatment intelligently.

The observational material is summarized in Table 1. The data were obtained in the cases of ten children with nephrosis during the stage of general anasarca and on four dogs which had been allowed to develop nutritional edema. One group of children received injections of serum; in one case the serum was unconcentrated, and in the other cases it was concentrated either by the lyophile process or by evaporation in a collodion bag. Another group of children were given acacia. The dogs received injections of concentrated homologous serum albumin.

· TABLE 1

Summary of Data

Pt.	Age.	Initial albumin.	Type of injection.	Amount protein or acacia.	Doses.	Days.	Diuresis, as loss in body wt.
	yrs.	Gm. %		Gm.			%
S. S.	3	1.55	Lyophile serum	11	1	1	0
W. S.	2	....	Lyophile serum	11	2	2	0
M. D.	5	1.54	Lyophile serum	12	1	1	16
J. J.	3	1.46	Lyophile serum	24	3	3	0
W. S.	2	....	Lyophile serum	29	5	5	0
R. V.	3	1.31	Evaporated serum	54	5	5	0
A. F.	8	0.83	Unconcentrated serum	65	6	3	0
F. D.	3	1.31	Acacia	14	1	1	23
J. C.	3	0.87	Acacia	18	1	1	0
N. S.	4	1.10	Acacia	36	2	3	19*
J. F.	6	0.92	Acacia	36	2	2	0
Dogs	2–3	1.30	Concentrated albumin	6	1	1	8*
	2–07	0.99	Concentrated albumin	10	1	1	18
	8–40	0.88	Concentrated albumin	15	2	3	11
	2–05	1.37	Concentrated albumin	15	1	1	6

* Loss in weight began before treatment was administered.

· In each group the cases are arranged in order in the table according to the *total amount* of protein or acacia administered. This total amount was sometimes given in divided doses over a period of days. In only one of the patients who received serum was diuresis accomplished; this child was given a single injection and the total amount of serum protein administered was not large. Diuresis took place in two of the four acacia cases, but in one of these subsequent inspection of the chart indicated that the kidneys had already started the process of removing fluid before the acacia was given. All of the dogs exhibited some degree of diuresis, although again in one instance spontaneous elimination had begun before the therapy was applied.

Figure 104 portrays the single case in which serum was successful in initiating diuresis. Seventy cubic centimeters of lyophile serum, which had been concentrated threefold, was injected, that is, the equivalent of 200 cc. of unconcentrated serum. Analyses were made of the patient's serum just before and one hour after the injection. The albumin concentration
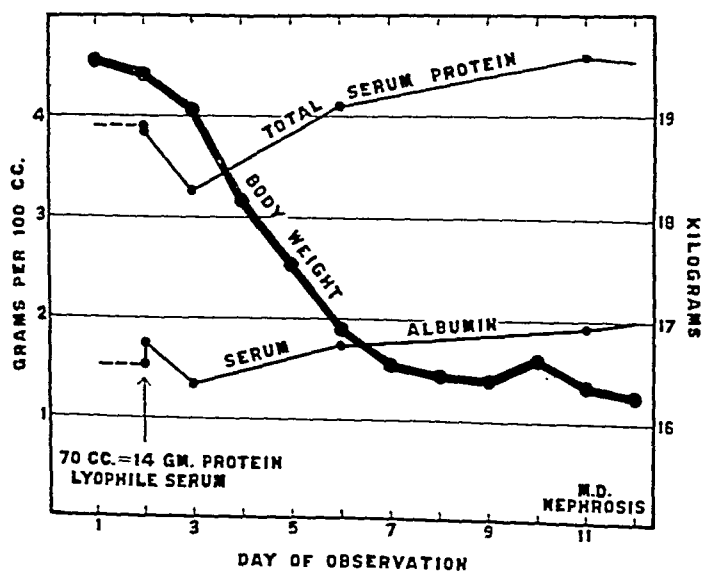
Fig. 104.—Diuresis initiated by serum.
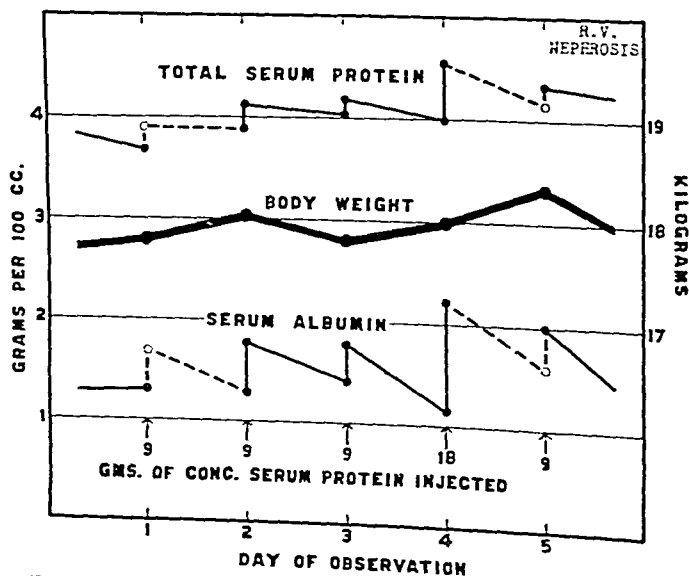
Fig. 105.—Course of events in the case of a three-year-old nephrotic patient with generalized anasarca following multiple injections of concentrated serum. The broken portions of the lines depicting serum protein concentration cover periods when no analyses were performed.

increased only 0.2 per cent and the globulin fell by more than this amount, so that a slight decrease in total protein was recorded. Nevertheless, diuresis set in and continued until a little more than 3 kg. of fluid had been eliminated. It is difficult to relate the diuresis to subsequent change in the serum since albumin concentration actually fell for twenty-four hours before rising gradually. The chart covers a period of twelve days. During the next month the edema reaccumulated even though the albumin level remained in the neighborhood of 2 per cent.
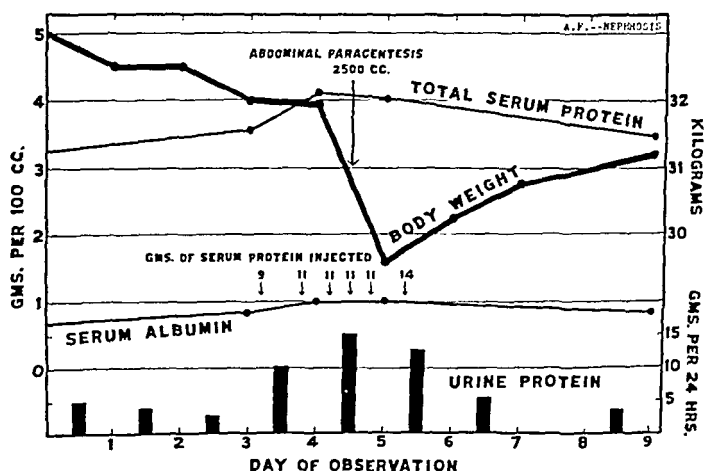
Fig. 106.—Record of patient receiving 6 injections of unconcentrated serum in three days.

Figure 105 shows the course of events in the case of a three-year-old boy who failed to develop diuresis after multiple injections of serum concentrated by evaporation. The injections were given over a period of five days. The 9 gm. of serum protein given in most of the injections is the equivalent of 150 cc. of unconcentrated serum; it was given in a volume of 40 cc. One transfusion consisted of 18 gm. The evanescent character of the slight changes in the patient's serum albumin is shown clearly. However, the daily fluctuations in serum albumin concentrations are as great and sometimes greater in this patient who failed to respond by diuresis as in the previous patient who did respond.

We have in Fig. 106 the record of a patient who received six injections of unconcentrated serum within three days. The total volume of transfused serum was 920 cc.; this serum furnished 65 gm. of serum protein, of which 45 gm. were albumin. The amount of albumin injected was roughly six or seven times as great as that originally present in the patient's circulation. Analyses of the patient's serum, which were made each morning before the injections, disclose extraordinarily little fluctuation in the serum albumin level. The excretion of protein in the urine was studied before, during, and after the period of transfusions. During the preceding three days the urinary protein varied from about 3 to 5 gm. During the transfusions it ranged from 10 to 15 gm., but promptly returned to the previous level when the injections were discontinued. We see that a large part of the injected serum appears to have been lost quickly in the urine.

These charts of illustrative cases fail to show differences which allow an understanding of why one patient exhibited diuresis while the others did not. Nor is there evidence of a general effect of sufficient magnitude or duration to provide a satisfying explanation of why diuresis might develop in a favorable case. The immediate effect of transfusing serum on the level of albumin in the recipient's plasma is usually small and always transient. Because the water-attracting property of serum depends upon its colloid osmotic pressure, which is determined to some extent by globulin concentration as well as by albumin, we have made estimates of this pressure using the formula of Wells, Youmans, and Miller.[2] Data are available for five transfusions in children and four transfusions in dogs in which analyses were made before, one hour after, and twenty-four hours after, the injection. These data are presented in Table 2. In some cases transfusion was followed by a fall in osmotic pressure; in others the pressure remained stationary; and in one dog only was a significant rise recorded. The average figures show an initial osmotic pressure of 117 mm. of water, a value of 124 mm. immediately after transfusion, and a return to the initial value within twenty-four hours. When we recall that normal osmotic pressure is usually in excess of 300 mm. of water, these variations cannot be regarded as significant.

There can be no doubt that the treatment of nephrosis with serum or with acacia was first undertaken with the thought that these measures might provide immediate relief from low osmotic pressure in the circulation. In view of the actual findings and because diuresis *does* sometimes result, it is necessary to look elsewhere for the reason.

Table 3 records a phenomenon which has been observed without exception following injections of acacia and after all types of serum transfusions: Hematocrit readings are shown before and at a variable number of minutes or hours after the

TABLE 2

Effect of Serum Intravenously on Calculated Colloid Osmotic Pressure

Cases.	Colloid osmotic pressure.		
	Before injection.	After injection.	
		1 hour.	24 hours.
	mm. water	mm. water	mm. water
2–07	93	94	93
8–40	105	115	110
J. J.	108	106	94
2–3	111	114	122
R. V.	113	131	120
M. D.	119	122	95
R. V.	120	133	112
J. J.	121	106	108
2–05	160	193	202
Average	117	124	117

injections. In all of the nineteen instances in which the observations were made a decrease in relative red cell volume followed the injections. The decrease varied from 1.7 to about 10 per cent and averaged 6.0 per cent. Now, it is possible to conceive of *three* mechanisms which might account for falls of this type in the hematocrit reading: (1) removal of red cells from the circulation, (2) shrinkage in the volume of individual red cells, and (3) increase in the volume of the plasma. That red cells are withdrawn from the blood stream appears unlikely since the maximal effect is observed when measurements are

made within as short a time às ten or fifteen minutes.   The only organ of the body which would seem to be able to withdraw red cells rapidly from the circulation is the spleen; we have observed the same type of hematocrit drop in the splenectomized animal.   Shrinkage in the volume of individual red cells has not been excluded, but since such shrinkage implies an increase in the electrolytes of plasma, it too is an unlikely

TABLE 3

The Immediate Effect on the Relative Volume of the Red Cells of Injection of Acacia or Transfusion with Serum

Patient.	Relative red cell volume.			Blood volume increase $\frac{h_1 - h_2}{h_2} \times 100$
	Before injection h_1	After injection h_2	Decrease $h_1 - h_2$	
	per cent	per cent	per cent	per cent
R. V.	33.2	31.5	1 7	5
J. J.	36.6	32.6	4.0	12
R. V.	31.5	28.0	3.5	13
R. V.	26.2	23.2	3.0	13
8–40	29.0	25.4	3.6	14
R. V.	30.2	26.0	4 2	16
J. J.	39.2	33.6	5 6	17
J. F.	35.1	29.3	5 8	20
F. D.	30.3	24 8	5.5	22
2–3	41.2	33.9	7.3	22
S. S.	31.5	25.6	5.9	23
J. J.	43.3	34.8	8 5	24
R. V.	30.6	24.1	6.5	27
N. S.	37.7	29.8	7.9	27
2–05	35.8	28.0	7.8	28
M. D.	35.4	27.4	8.0	29
J. C.	36.0	26.5	9.5	36
8–40	23.0	16.9	6.1	36
2–07	30.9	20 8	10.1	49
Average	33.5	27.5	6.0	23

cause.   The electrolytes of the plasma in these cases are in equilibrium with large reservoirs of edema fluid and their concentration is not easily altered.   If we accept for the moment the reasonable explanation that the fall in hematocrit is an expression of increased plasma volume, it is pertinent to point out that the hematocrit readings alone permit an estimate of the percentage increase in the volume of the blood, that is, the

percentage increase can be calculated even without any knowledge of the actual blood volume. The estimates, which appear in the last column, indicate increases in blood volume of from 5 to 49 per cent (average 23 per cent). The increases then are large; with any reasonable assumption for actual blood volume, the size of the increment greatly exceeds the volume of fluid administered during the injection. That is to say, most of the fluid added to the circulation must have been taken from the huge supplies in the interstitial tissues.

In four dogs an attempt was made by the dye technic to measure *blood volume* before and after the injections. In spite of technical difficulties, reasonably satisfactory readings were obtained in three of the experiments (Table 4). An appreci-

TABLE 4

Measurements of Blood Volume by Dye Technic

Dog.	Blood volume.		
	Before injection.	After injection.	Increase.
	cc.	cc.	per cent
2–07	917	967	6
8–41	1535	1880	23
8–42	1368	1777	30
Average	1273	1541	20

able increase in blood volume was recorded as having occurred during the hour following the albumin injection. The average increase was 21 per cent of the original blood volume, a value in line with our estimate from examining the fall in hematocrit level.

One other means of forming an estimate of the volume shift in the circulation is available: From a knowledge of the amount of protein in the injected serum and its effect on concentration in the recipient's plasma, it is possible to calculate the circulatory volumes before and after the injection. That is, one can look upon the therapeutic serum as if it were a dye injected for the purpose of determining blood volume. We have seen, however, that much of the injected protein soon finds its way

into the urine. This method, then, can be expected to yield a reasonable estimate of blood volume only if analyses are made within a very brief period following the injection. For three transfusions in one of our patients this condition was fulfilled, that is, the interval between injection and analytical sample was only ten to twenty minutes. The results of the blood volume determinations for this patient are shown in Table 5. The values for initial blood volume, which vary from 6.1 to 7.4 per cent of the body weight, are in reasonable agreement and fall within a range which other investigators, using different methods, have found in edematous patients. The magnitude of the blood volume shift is apparent by comparing the values before and after the injection.

TABLE 5

PATIENT R. V. EFFECT OF SERUM INJECTION ON BLOOD VOLUME

Blood volume.		Interval between injection and sample.	Amount of serum protein injected.	Original blood volume relative to body weight.
Before injection.	After injection.			
cc.	cc.	minutes	grams	per cent
1336	1502	20	9	7.4
1182	1372	10	9	6.7
1102	1400	20	18	6.1

On the basis of the evidence presented, we have become convinced that *some increase* in blood volume always ensues when serum or acacia is injected into the circulation. The magnitude of the increase is usually so great as to prevent effectively any significant change in the colloid osmotic pressure of the plasma. Since this is so, it is reasonable to inquire if the blood volume increase may not be the direct cause of diuresis when this phenomenon follows. Support for a positive answer to the inquiry is found in an experiment outlined in Fig. 107.

Dog 2–07 had been allowed to develop nutritional hypoproteinemia for fifty-eight days. The serum albumin fell to less than 1 per cent and ascites developed. At this point diuresis was invoked by transfusing a solution of concentrated

serum albumin. The hematocrit revealed the usual drop indic-ative of expansion in the volume of the blood; the diuresis lasted for three days. Then the body weight again rose as edema re-accumulated. At this point, the sixty-fifth experi-mental day, a second transfusion was given with 290 cc. of red cells which had been washed to remove adherent plasma. This procedure can be assumed to have increased the volume of the blood since no concentrating effect was observed on the protein level in the plasma. We note that it too was followed by diu-
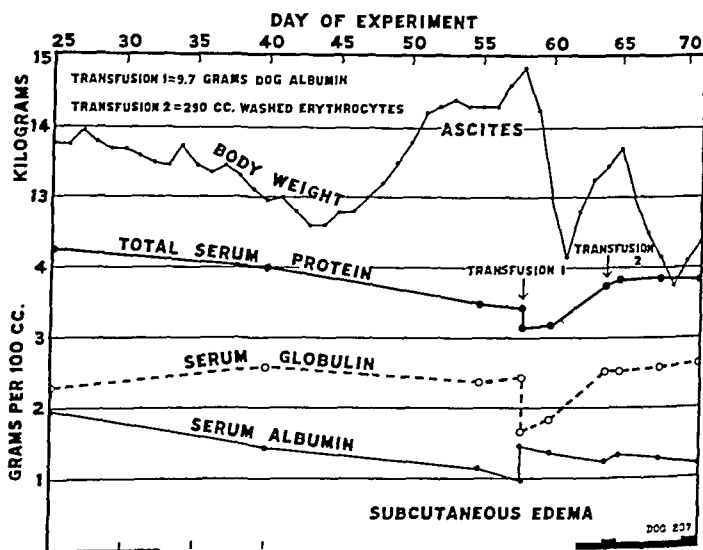
Fig. 107.—The reaction of an edematous dog to transfusion: (1) with concentrated serum albumin, and (2) with a suspension of red blood cells. (From the Bull. N. Y. Acad. Med., second series, 15: 83, 1939.)

resis which lasted for four days. If, then, we are permitted to assume that the mechanism of diuresis was the same after both of these injections, the inference is strong that the *inciting* fac-tor was the enlarged blood volume. Just how this factor oper-ates to provoke diuresis can only be guessed from our data. The circulatory increment must be accommodated somewhere in the vascular system, presumably by dilatation of capillaries. It is conceivable that the vessels of the kidney may be particu-larly affected and so increase the rate of urine formation.

Comment.—The material which we have analyzed is not the kind from which a series of conclusions should be drawn. It does, however, give rise to several questions which should be considered in further attempts to evaluate these modes of therapy:

1. Except for convenience in transportation and preservation, is anything gained by concentration?   Concentrated serum, when injected into the circulation, is diluted at once *in vivo*. The fluid required to effect this dilution cannot have an appreciable effect on the huge stores of water in the tissues and serous cavities.

2. Are large single injections to be preferred to multiple small injections?   Our data indicate that large transfusions have a greater effect in increasing blood volume than small transfusions.   It may therefore be suspected that they produce a greater stimulus toward diuresis.   Small transfusions, on the other hand, are attended by less systemic reaction; it may well be that the attempt to avoid such reactions will defeat the purpose of the therapy.

3. Is it justifiable to discard the red cells and inject only the serum?   Most of these patients suffer from some degree of anemia; after the injection of serum they become relatively more anemic.   It would seem the part of wisdom to administer enough of the red cells to prevent the fall in the hematocrit reading.   The red cells also serve to increase the blood volume, they are not so readily excreted in the urine as serum, and their action in promoting diuresis may well be expected to enhance the effect of serum alone.

BIBLIOGRAPHY

1. (a) Hartmann, A. F., Senn, M. J. E., Nelson, M V., and Perley, A. M.: The Use of Acacia in the Treatment of Edema.   J.A.M.A., 100: 251, 1933.

(b) Aldrich, C. A., Stokes, J., Jr., Killingsworth, W. P., and McGuiness, A. C.: Concentrated Human Blood Serum as a Diuretic in the Treatment of Nephrosis.   J.A.M.A., 111: 129, 1938.

2. Wells, H. S., Youmans, J. B., and Miller. D. G., Jr.: A Formula and Nomogram for the Estimation of the Osmotic Pressure of Colloids from the Albumin and Total Protein Concentrations of Human Blood Sera.   J. Clin. Investigation, 12: 1103, 1933.
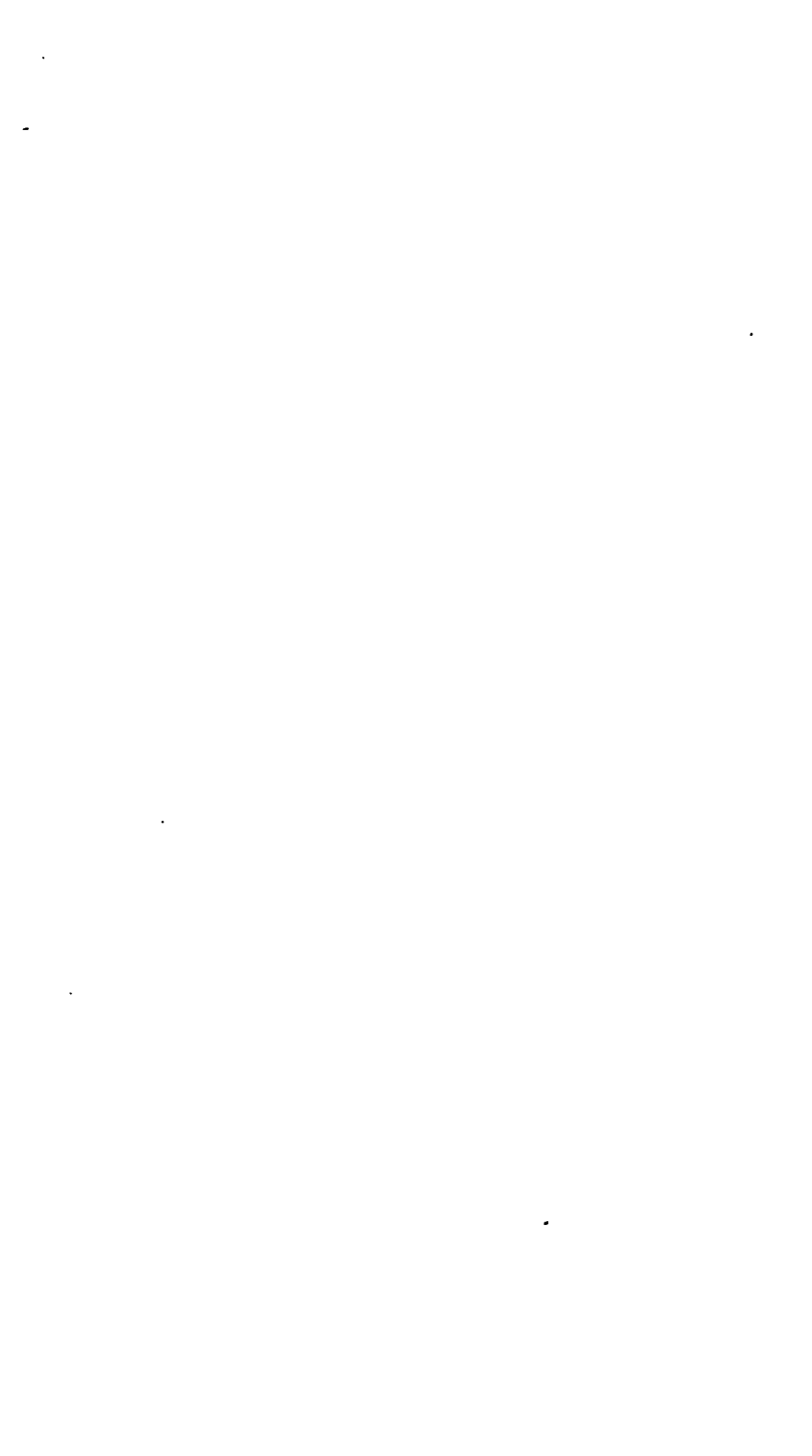
CLINIC OF DR. THOMAS H. McGAVACK

DEPARTMENT OF MEDICINE, NEW YORK MEDICAL COLLEGE
AND THE MEDICAL SERVICES, FLOWER AND FIFTH AVENUE,
AND METROPOLITAN HOSPITALS

ACETYL-BETA-METHYLCHOLINE AS A THERAPEUTIC AGENT

CHEMICALLY, acetyl-beta-methylcholine chloride is a derivative of acetylcholine. While it has similar pharmacologic effects, there are some striking differences which enhance its value as a therapeutic agent: It has the advantage of being effective *per os.* It is more slowly destroyed in the body. The "nicotine"-like action is slight, whereas the "muscarine" effect is marked. Pharmacodynamically, therefore, one observes *three main spheres of influence:* (1) an inhibition of the heart with slowing; (2) a peripheral vasodilatation with a lowering of blood pressure; and (3) a furthering action upon the smooth muscle of the bronchi, stomach, intestines, bladder and uterus. These changes are obviously the opposite of those obtained by sympathetic stimulation; hence, the drug may be described as a "pharmacologic antagonist" to epinephrine. Its effects may be promptly abolished by atropine.

Rules in Applying the Drug.—The drug is effective *by mouth* in amounts ranging from 50 to 1500 mg.; by *subcutaneous injection* in amounts from 10 to 40 mg., and by *iontophoresis* in from 0.2 to 1.0 per cent solutions. Absorption from the subcutaneous tissues is rapid and this obviates the necessity for intravenous administration, which may be attended by severe cardiac irregularities and even arrest. *Overdosage* is followed by generalized flushing, profuse sweating, palpitation, salivation, lowering of blood pressure, and intestinal cramps.

In applying the drug, certain simple rules should be observed to obtain a maximum therapeutic influence and a mini-

mum of unpleasant side effects. *Severe coronary sclerosis and a history of asthma are contraindications,* or at least represent signals for caution in its application. We have seen precordial pain produced during the use of the drug by iontophoresis for varicose ulcers in individuals known to be suffering from arteriosclerotic heart disease. The patient should be lying down to offset the effects of lowered blood pressure caused when it is employed parenterally. Should unpleasant symptoms follow its subcutaneous administration, a tourniquet placed above the site of injection will diminish the intensity of the action by decreasing absorption. Conversely, vigorous massage of the site of application will accelerate absorption and intensify action. This procedure is particularly useful in the management of auricular paroxysmal tachycardia where the peripheral circulation may at times be retarded or even inadequate.

Inasmuch as the range of dosage is very wide, the patient should be watched for *toxic manifestations,* the most serious of which is *cardiac arrest.* Starr[1] has seen a systole lasting for seventy seconds. One one-hundred-fiftieth (1/150) grain of atropine sulfate, intravenously, immediately abolishes the mecholyl effects, and terminates them within a few moments when injected subcutaneously.

The muscarine action of acetyl-beta-methylcholine has been made the basis for its trial as a therapeutic agent in clinical medicine. The peripheral vasodilatation has prompted its application in *arthritis*[2, 3, 4, 5] and a wide variety of *disturbances in the blood vessels*[2, 3, 4, 6, 7, 8, 9, 10, 11, 12]; the inhibitory effect upon the heart, its use in the *cardiac arrhythmias*[1, 13, 14]; and the stimulative action on involuntary musculature, its administration in *postoperative intestinal paresis* and in various abdominal conditions associated with *sympatheticotonia.*[15, 16]

Peripheral Vascular Disease.—The beneficial action of choline and its derivatives upon diseases of peripheral vascular origin is directly dependent upon the ability of such drugs to relax vascular spasm, to produce a regional diaphoresis, and to relieve anoxemia, thus promoting the removal of waste products and increasing the local circulation.

In view of the fact that these agents are rapidly destroyed by blood and tissues, any *local effect from their administration*

orally or *subcutaneously* is very transient and demands the use of amounts sufficiently large to produce the uncomfortable, and at times harmful, manifestations. Prolonged action and high local concentration have been achieved through the application of acetyl-beta-methylcholine chloride by *iontophoresis* to the affected parts. The technic of such administration has been repeatedly described[2, 3, 4, 5] and needs no reiteration here. Effects from a single application last for from two to six hours, and permanent results can at times be obtained by repeated treatment. In several thousand treatments of not more than forty-five minutes' duration, using concentrations of 0.20 per cent, we have observed no severe systemic reactions. One patient with electrocardiographic evidence of coronary sclerosis has shown mild precordial pain, lasting for as long as two hours, and in one case flushing of the face and mild intestinal cramps occurred toward the end of the treatment.

1. VARICOSE ULCERS.—The most dramatic responses to acetyl-beta-methylcholine chloride therapy have been achieved in the treatment of varicose ulcers.[2, 3, 6, 11] Some workers have not obtained such gratifying results.[10] Of sixty-one cases seen in this clinic which were resistant to all of the usual forms of ambulatory and hospital therapy, there have been complete failures in but three: (1) the case of a twenty-two-year-old man, showing the body build of a eumorphic giant, in which spontaneously appearing ulcers of six years' duration were present and in which a deep phlebitis and a constitutionally inferior background may have existed; (2) the case of a seventy-one-year-old man with longstanding cardiac disease, chronic passive congestion, and ulcers open for twenty years; and (3) that of a man, aged seventy-three, who had a traumatic ulcer of twenty-two years' duration over the anterior surface of the middle third of the right shin bone.

Iontophoresis with acetyl-beta-methylcholine routinely and consistently effects a rapid *relief of pain*, the *disappearance of lymphedema*, the *abatement of superficial infection*, and the *development of a healthy granulating surface*. These effects appear to be totally independent of the pathologic background upon which the ulcer has occurred. Simple varicose veins, deep thrombophlebitis, syphilis, diabetes, coexisting cellulitis, and so forth, may play some part in the number of treatments neces-

sary to bring about the above-mentioned changes, but only in rare instances prevent their ultimate appearance. Even in the face of widespread scarring and exposed tendons and bone, healing of the ulcers has been accomplished:

W. R., a sixty-two-year-old white male, had varicose veins and saphenous incompetence of twenty-five years' duration. Following a slight injury to the inner side of the right ankle, he developed a small ulcer which, under the use of a patent medicine salve, became a lesion 11 by 7.5 cm. in size, at the base of which the edge of the internal malleolus and the tendons immediately below it were laid bare for a distance of 1.5 cm. The patient first came under our observation four months after this condition began, at which time there was some infection of the tendon sheath and an inflammatory reaction within the tendon itself. The ulcer showed a dirty, non-granulating, lardaceous base.

This wound has been completely closed after five and one-half months of treatment with acetyl-beta-methylcholine chloride combined with the use of pressure bandages and routine surgical hygiene. In all, 112 treatments have been given—daily for one-half hour during the first two months, and then three times weekly. Following healing of the ulcer, saphenous ligation has been done bilaterally.

Similar use has been made of the method in cases with *diffuse cellulitis* in which it seemed advisable to delay surgical therapy; in the very *obese* where infection is common after saphenous vein ligation, and particularly in the face of an active *thrombophlebitis;* in instances of *saphenous incompetency* and deep thrombophlebitis resistant to other forms of therapy, and not amenable to surgical procedure; and so forth.

The method is not recommended as the *only* therapeutic measure in the management of varicose ulcers, but should be rationalized in conjunction with other measures.[11] For instance, among our cases have been those of patients with encircling ulcers in which skin grafting had repeatedly failed prior to the use of acetyl-beta-methylcholine. Moreover, in the largest ulcers with marked scar tissue formation, we have found skin grafting successful following the use of acetyl-beta-methylcholine when it had failed previously. *Traumatic ulcers,* particularly those associated with compound fractures of the tibia or in which erosion of a large area of skin over the tibia exists, have proven the most difficult and, in our hands, some form of skin grafting has always been used in connection with the iontophoresis therapy. The following case is illustrative:

F. K., aged fifty-five, was admitted to the hospital for treatment of an ulcer measuring 9 by 7.5 cm. on the anterior surface of the right leg in its middle third. This ulcer followed a compound fracture of the right leg fourteen years before and had never been healed, although all the usual forms of therapy had been tried. Two weeks following admission, after the wound had been made as aseptic as possible, seed grafting was attempted, but without any success whatsoever. Three weeks later, mecholyl by iontophoresis was used. The patient was given a thirty-minute treatment with an 0.2 per cent solution and a current of 10 to 15 milliamperes. Treatments were repeated three times weekly to a total of seventeen.

At the end of this time the base of the ulcer showed a healthy granulating surface. Seed grafts were again attempted and resulted in closure of the entire surface with the exception of an area 0.5 cm. in size over the anterior region of the tibia. Acetyl-beta-methylcholine treatment was used after as well as before this grafting to insure the maintenance of as rich a blood supply as possible.

2. DEEP THROMBOPHLEBITIS.—Several reports of the successful application of acetyl-beta-methylcholine by iontophoresis to deep thrombophlebitis have appeared in the literature.[3, 7, 12] Our experience is not wholly gratifying although treatment has usually been attended by symptomatic relief, and persistent application from two to five times weekly has caused some disappearance of the associated lymphedema. In any instance it is doubtful whether a fundamental change has been produced in the underlying pathologic process. A case in point is as follows:

M. H., a white female, twenty-nine years old, following pelvic inflammatory disease six years previously, developed a deep thrombophlebitis and lymphedema of the right leg and thigh. Measurements showed a circumference greater by 2 inches in this thigh and calf than in the left. Following twenty-nine treatments with acetyl-beta-methylcholine chloride (0.2 per cent solution three times weekly), using a current of 15 to 20 milliamperes, the right leg still measured 1½ inches larger than the left. However, the patient obtained relief of "fulness, heaviness, and dull aching." Such relief was noticed after the first treatment; this lasted, however, for only one to three hours. As treatments continued, she found the period of relief longer, until it was possible to obtain freedom from symptoms if a regimen of three treatments weekly was followed.

3. RAYNAUD'S SYNDROME, WITH AND WITHOUT SCLERODERMA.—The results attending the application of mecholyl to cases of Raynaud's disease would appear to vary *directly* as to the spasm and *inversely* as to the local organic change present in the digital arteries. The drug has proved useful by

mouth,[13, 17, 18] but still more valuable by iontophoresis.[2, 6, 19] Kovacs, Saylor and Wright[19] report gratifying results in twelve cases, in six of which there was a complicating scleroderma. Starr[13] saw relief in four individuals when the drug was administered either by mouth or subcutaneously. Temporary lowering of surface temperatures, ascribed to the blood pressure effects, was usually followed by vasodilatation and an increase in surface temperature. We have observed a similar increase in spasm and lowering of temperature immediately after iontophoresis, but usually an elevation of skin temperature and disappearance of the attack within thirty minutes after discontinuing treatment. These negative phases have been eliminated by *shortening* the treatments and by keeping the current at or below *10 milliamperes.*

The following observations are interesting and suggest that acetyl-beta-methylcholine chloride by iontophoresis may produce a phase in which an adrenalin influence is prominent before vasodilatation and other beneficial effects appear:

E. W., a fifty-one-year-old female of the hypoplastic type, developed Raynaud's syndrome following a septicemia three years previously. When first seen there was gangrene of the lateral surface of the distal phalanx of the left forefinger and superficial cracking and ulceration of the tips of all the fingers. Skin temperature studies of the fingers, before and after nerve block, showed only a partial response. The gangrenous area cleared and all symptoms were relieved by forty-seven treatments with acetyl-beta-methylcholine by iontophoresis. However, despite the fact that milliamperage was kept below 10 and treatments were never given for longer than thirty minutes, each treatment was attended by increased spasm, blanching of the fingers, and an elevation of from 10 to 40 points in the systolic blood pressure. Disappearance of these phenomena began immediately after each treatment was finished, and increased skin temperatures, vasodilatation, and blood pressures below the initial values have always been present within fifteen minutes thereafter and have persisted for several hours if the patient was not exposed to cold (temperatures below 62° F.).

In our experience no patient with Raynaud's disease has been cured by iontophoresis with acetyl-beta-methylcholine chloride, but superficial ulcerations and gangrenous areas, for which operation had been advised, have been completely healed. All patients have obtained prompt symptomatic relief and after a number of treatments have shown an increased tolerance for cold.

4. OCCLUSIVE TYPES OF PERIPHERAL VASCULAR DISEASE.—
No widespread trial of acetyl-beta-methylcholine chloride has
been made in organic types of peripheral vascular disease, al-
though some observations are on record.[4, 8, 19] It would seem
wise to apply the treatment only after skin temperature re-
sponses to reflex stimulation, or to nerve block, have shown the
presence of a reasonable degree of spasm. We believe *typhoid
vaccine* probably more satisfactory in thrombo-angiitis obliter-
ans, and various forms of *physiotherapy*, particularly heat
(90° F.) and intermittent venous occlusion, more desirable in
arteriosclerosis.

The use of mecholyl subcutaneously in cases of organic dis-
ease may defeat its own purpose by lowering the blood pres-
sure.[1] Lowering of skin temperatures has been observed fol-
lowing subcutaneous injection in such instances—a fact which
is probably related to a diminished head of pressure in the
peripheral arteries associated with a compensatory vasocon-
striction. In this clinic, a drop in blood pressure has been
noted when the drug has been applied by iontophoresis in ar-
teriosclerosis and advanced thrombo-angiitis obliterans. *Its
routine use is not advised.*

5. HYPERTENSION.—Acetyl-beta-methylcholine has been
employed in hypertension on the basis that high blood pressure
is the result of an increased peripheral vascular tone. In nearly
all instances there is a "marked to moderate decrease in blood
pressure" subsequent to its administration.[9] A sustained effect,
however, seems unlikely, irrespective of the mode of adminis-
tration. The unpleasant symptoms following subcutaneous
injection have far outweighed any beneficial action.[13] No ap-
preciable change from prolonged use of the drug by mouth has
been observed. In order to influence the blood pressure suffi-
cient mecholyl must be given to produce a generalized systemic
reaction. Therefore iontophoresis is the *least* desirable method
of administration.

While no personal experience with the drug has been had
in this connection, it seems safe to conclude that its application
clinically to hyperpiesis is hardly justified, although experi-
mentation should be carried further before final judgment is
passed.

Arthritis.—Circulatory disturbances have been shown to play an important part in the pathologic physiology underlying all forms of arthritis.[21, 22] A diminution in the blood flow in and about affected joints has been proved, and an overlying constriction of small vessels and capillaries is the rule. As a result, slow response to environmental conditions are to be observed. These changes are greater in the rheumatoid than in osteo-arthritic forms of the disease.

Several authors have reported beneficial effects in any and all types of arthritis. Kiel[4] distinguishes *rheumatoid* and the *osteo-arthritic* forms, finding 55 per cent of the former and 17 per cent of the latter completely relieved of symptoms. An additional 33 per cent and 43 per cent, respectively, were partially relieved. He concludes that "end results in the rheumatoid group are encouraging." Kovacs and Kovacs[22] made somewhat similar observations. Abel[23] found equally good results in both proliferative and degenerative forms of arthritis. No very satisfactory criteria have as yet been evolved for determining which cases will respond and which will not, but the work of Kovacs and his associates[20] may later point the way.

We have observed improvement in extremely advanced conditions, such as psoriatic atrophic arthritis with nearly complete immobilization of all the joints of the extremities and a superimposed scleroderma. On the other hand, we have often failed to obtain more than very transient relief (half hour) in the mildest cases of either the rheumatoid or osteo-arthritic forms.

Iontophoresis is the method of choice for applying mecholyl in arthritis, and the results in many instances are striking:

G. W., a fifty-six-year-old woman, suffered from chronic osteo-arthritis for at least sixteen years, the condition particularly involving both knee joints. There was roentgenologic evidence of advanced bony proliferation with lipping of the articular ends of the femur and tibia and a marked narrowing of the joint spaces. Similar changes were present in the patella. The left knee had a restricted range of motion. For eight years this patient had required daily sedation to control pain and, when first seen, was taking from 40 to 60 grains of sodium salicylate daily, and at times 1 to 3 grains of codeine sulfate in addition.

Her response to acetyl-beta-methylcholine by iontophoresis was prompt and striking, relief of pain occurring following the first treatment. Sedation was discontinued after the use of daily treatments for one week. Six weeks of such therapy at thrice weekly intervals were followed by a period of three

months with complete freedom from pain. She has been maintained in a symptom-free condition by the use of treatments three times weekly for four- to six-week periods, repeated every four to six months.

Apparently similar cases have shown practically no beneficial effects:

G. C., a white female sixty-eight years old, has suffered for eight years from an osteo-arthritis, prominently involving both knees, with roentgenologic evidence of decreased joint spaces and proliferative changes about the patella and the articular ends of both femurs and tibias. Her pain has intermittently demanded sedation, chiefly aspirin, but at times opiates. There has been reasonable freedom of motion about both joints, but extremes of flexion or extension have been attended by severe pain. This case appears in every particular similar to that of G. W. mentioned above. However, the present patient obtained no permanent relief whatsoever from acetyl-beta-methylcholine therapy persistently tried. Slight amelioration of pain in the knees for one-half hour following each treatment has been observed at times.

Indications for the drug in arthritis need further delineation, but its beneficial effects in a reasonable percentage of cases justify further trial.

The Cardiac Arrhythmias.—Because of its vagal inhibitory effect, acetyl-beta-methylcholine should theoretically prove of definite value in the management of auricular paroxysmal tachycardia, auricular flutter, and auricular fibrillation. In actuality its application, save in the first mentioned condition, has proved to be rather disappointing.

It was Starr[13] who first showed that acetyl-beta-methylcholine, by its stimulation of the parasympathetic nerves, may promptly terminate an attack of paroxysmal auricular tachycardia. Nodal as well as other forms may respond.[14] Starr[1] has reported the cessation of sixty-six of seventy-five attacks in thirty-seven patients following its use. In each instance, carotid sinus pressure had been unsuccessfully tried before mecholyl was used. Scherf and Boyd[24] strongly emphasize the importance of *vagal stimulation* in controlling the attacks, and urge that all reflex pathways be tried before resort is had to medicinal therapy, for "in one patient one reflex, and in another, another may be effective."

1. PAROXYSMAL AURICULAR TACHYCARDIA.—While results have not been as favorable with this drug in our experience as in that reported by Starr,[1, 13] it has more often succeeded than

failed in the resistant case of supraventricular paroxysmal tachycardia.

In view of the fact that the injection of acetyl-beta-methyl-choline is not unattended by the danger of cardiac arrest, it is believed that it *should not be employed at all* unless the patient is imminently in danger of acute heart failure or actually showing signs thereof.

The *dosage* should be regulated according to age and weight —the older and heavier the person, the greater the amount of drug necessary. Young people react very much more vigorously, and as little as 10 mg. may stop an attack, whereas 30 mg. repeated in one-half hour have been necessary in a much overweight woman of sixty-six years. The *average* successful dose has been 30 mg. given subcutaneously. Some attention to the details already described will often end in success, where dependence upon injection alone will fail.

It is important to have at hand a syringe loaded with 1/150 grain of *atropine sulfate*. This may be given the moment a regular rhythm has been established, thus eliminating any further unpleasant effects from the choline preparation. Even more urgent is the immediate need for *atropine* in the individual in whom asystole has developed. We feel that a needle should be inserted into the vein before acetyl-beta-methyl-choline is administered, and salt solution slowly injected. Should *asystole* occur during or following the injection of mecholyl, a quick switch to the atropine syringe should be made and the contents emptied into the vein. It is wise to massage toward the heart to facilitate rapid admixture with the already slowed blood stream.

In the average case, *flushing* of the neck and face will appear in about a minute after injection of acetyl-beta-methyl-choline. A few seconds later, various *transient irregularities* in cardiac action occur, such as prolonged conduction, momentary periods of asystole, extrasystoles, variations in intensity of heart sounds, weakness of the pulse, and lowering of blood pressure. Increased depth of breathing, sweating, and salivation usually accompany. In a few minutes, a reversion to normal rhythm is seen in the successfully treated case. If an attack does not stop promptly after the appearance of the flush, then the site of injection should be massaged vigorously,

and pressure made *alternately* over the carotid sinuses. Should these methods fail, the drug may be repeated in a *larger* dose as soon as its effects have worn off—that is, in about fifteen to twenty minutes. This technic has been effective in relieving two-thirds of the cases in which we have failed to obtain a response to reflex stimulation alone.

As a prophylactic against attacks the drug is of little or no value.

2. AURICULAR FLUTTER.—Auricular flutter is not as easy to control by mecholyl as is paroxysmal auricular tachycardia. Some degree of auriculoventricular block may be attained, but this is more frequently transient than permanent.[1] Occasionally, flutter will change to fibrillation and then to normal rhythm under the influence of the drug. However, its action in this condition is extremely uncertain. *Digitalis* or *quinidine* is much more dependable and always to be preferred.

3. AURICULAR FIBRILLATION.—While transient slowing of the heart has been seen following the administration of acetyl-beta-methylcholine in cases of auricular fibrillation, its use in this condition is hardly justifiable on either theoretical or practical grounds.

Abdominal Conditions.—Acetyl-beta-methylcholine chloride has been recommended by mouth, in doses ranging from 50 to 500 mg., for various abdominal conditions, including *postoperative distention,*[16] *atonic bladder,*[25] and *atonic colon.*[26] Inasmuch as the action is shortlived, repeated doses are frequently necessary and distressing symptoms are not uncommon. Temporary relief without unpleasant manifestations has been afforded patients with atonic conditions of the large bowel through the daily administration of mecholyl by iontophoresis over the abdomen. However, it would seem that most of its beneficial effects in abdominal conditions can be obtained in other ways without the danger of untoward reactions.

Other Conditions.—Acetyl-beta-methylcholine chloride has been recommended for a wide variety of diseases, but particularly those associated with autonomic nervous system imbalance. Jacoby[27] claims some degree of success in certain *dysmenorrheas* and in pelvic inflammatory disease. Erlanger[28] states that he has worked with mecholyl in certain *eye conditions,* but does not mention types of cases or actual results.

Starr[13] has suggested that the drug might be of value in *Ménière's syndrome*, and Cooper[29] has put this to the test of clinical investigation. In all, Cooper has reported six cases of Ménière's syndrome, five of which were "distinctly relieved in the majority of acute exacerbations" when the drug was administered orally in 80 mg. doses three times daily. On the basis of his results, he believes this choline derivative is not only useful for the attack, but also has a prophylactic value in reducing the number of attacks. In a single case of this condition in our hands, results following the administration of the drug were unsatisfactory.

Summary.—The therapeutic value of acetyl-beta-methylcholine has been appraised in peripheral vascular disorders, in arthritis, in several cardiac arrhythmias, and in some abdominal conditions.

The drug seems to warrant a place under certain conditions in the management of paroxysmal auricular tachycardia, Raynaud's disease, varicose ulcers, and arthritis.

BIBLIOGRAPHY

1. Starr, I., Jr.: Acetyl-beta-methylcholine. IV. Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm. Am. J. M. Sc., **191:** 210, 1936.

2. Kovacs, J.: The Iontophoresis of Acetyl-beta-methylcholine Chloride in the Treatment of Chronic Arthritis and Peripheral Vascular Disease. Am. J. M. Sc., **188:** 32, 1934.

3. Wright, I. S.: The Modern Treatment of Diseases of the Peripheral Vascular System. M. Clin. North America, **17:** 1429, 1934.

4. Kiel, O. B.: Acetyl-beta-methylcholine Chloride by Iontophoresis in the Treatment of Arthritis and Certain Peripheral Vascular Disturbances of the Extremities, Texas State J. Med., **34:** 530, 1938.

5. Mathae, G. H.: The Treatment of Arthritis with Mecholyl Iontophoresis. J. Missouri M. A., **33:** 303, 1936.

6. Saylor, L., Kovacs, J., Duryee, A. W., and Wright, I. S.: The Treatment of Chronic Varicose Ulcers by Means of Acetyl-beta-methylcholine Chloride Iontophoresis. J.A.M.A., **107:** 114, 1936.

7. Murphy, H. L.: The Treatment of Thrombophlebitis with Acetyl-beta-methylcholine Chloride Iontophoresis. Surg., Gynec. and Obst., **65:** 100, 1937.

8. Cohn, T., and Benson, S.: Iontophoresis of Acetyl-beta-methylcholine Chloride in Peripheral Vascular Diseases. Arch. Phys. Therapy, **18:** 583, 1937.

9. Engle, D. T., and Binger, M. W.: The Response in Blood Pressure of Hypertensive Patients to Acetyl-beta-methylcholine. Am. J. M. Sc., **198:** 609, 1939.

10. Baker, F.: Indications and Technic of Iontophoresis. Arch. Phys. Therapy, **20:** 197, 1939.

11. McGavack, T. H., and Samworth, R. P.: The Place of Iontophoresis with Acetyl-beta-methylcholine Chloride (Mecholyl) in the Treatment of Varicose Ulcers. Bull. New York M. Coll., Flower & Fifth Ave. Hosps., 2: 65, 1939.

12. Sokolov, R. A., and Meyers, M. P.: The Treatment of Deep Thrombophlebitis and Chronic Leg Ulcers with Acetyl-beta-methylcholine Chloride Iontophoresis. Am. Heart J., 17: 316, 1939.

13. Starr, I., Jr.: Acetyl-beta-methylcholine. III. Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease, with a Discussion of its Action in Other Conditions. Am. J. M. Sc., 186: 330, 1933.

14. Wright, F. H.: Paroxysmal Nodal Tachycardia Treated with Mecholyl. Am. J. Dis. Child., 56: 1334, 1938.

15. Staff, I., Jr., Elsom, K. A., Reisinger, J. A., and Richards, A. N.: Acetyl-beta-methylcholine. I. The Action on Normal Persons. Am. J. M. Sc., 186: 313, 1933.

16. Abbott, W. O.: Acetyl-betamethylcholine. II. The Action on the Gastro-Intestinal Tract of Normal Persons, in Abdominal Distention, and in Certain Other Conditions. Am. J. M. Sc., 186: 323, 1933.

17. Goldsmith, G. A.: The Vasodilating Effects of Acetyl-beta-methylcholine. Proc. Staff Meet., Mayo Clin., 9: 337, 1934.

18. Goldsmith, G. A.: The Effectiveness of Acetyl-beta-methylcholine Given by Mouth as a Vasodilating Agent. Ann. Int. Med., 9: 1196, 1936.

19. Kovacs, J., Saylor, L. L., and Wright, I. S.: The Pharmacologic and Therapeutic Effects of Certain Choline Compounds; Results in the Treatment of Hypertension, Arthritis, Organic Occlusive Vascular Disease, Raynaud's Disease, Scleroderma, and Varicose Ulcers. Am. Heart J., 11: 53, 1936.

20. Kovacs, J., Wright, I. S., and Duryee, A. W.: The Surface Temperature and the Minute Blood Vessels of the Skin in Arthritis. J.A.M.A., 100: 1018, 1933.

21. Pemberton, R.: Arthritis. In: Tice's Practice of Medicine, 6: 449, 1938. W. F. Prior Co., Hagerstown, Md.

22. Kovacs, R., and Kovacs, J.: Newer Aspects of Iontophoresis for Arthritis and Circulatory Disturbances. Arch. Phys. Therapy, 15: 593, 1934.

23. Abel, O., Jr.: The Use of Mecholyl in Arthritis. J. Missouri M. A., 32: 351, 1935.

24. Scherf, D., and Boyd, L. J.: Cardiovascular Diseases; Their Diagnosis and Treatment, C. V. Mosby Co., St. Louis, 1939.

25. Gernon, J. T., Palmer, E., and McKenna, C. M.: Some Recent Developments in the Treatment of Neurogenic Dysfunction of the Bladder, Based on Cystometry. J. Urol., 35: 515. 1936.

26. Ritvo, M.: Drugs as an Aid in Roentgen Examination of the Gastrointestinal Tract. Am. J. Roentgenol., 36: 868, 1936.

27. Jacoby, A.: The Treatment of Pelvic Inflammation by Iontophoresis of Acetyl-beta-methylcholine Chloride. Am. J. Obst. and Gynec., 31: 93, 1936.

28. Erlanger, G.: Iontophoretic Medication in Ophthalmology; Theoretic and Practical Aspects. Arch. Phys. Therapy, 20: 16, 1939.

29. Cooper, M. J.: Clinical Observations on the Effects of Choline Compounds in Neurologic Disorders, with Special Reference to Ménière's Syndrome. Am. J. M. Sc., 195: 83, 1938.

CLINIC OF DR. JOHN K. CURTIS

FIRST MEDICAL SERVICE, BELLEVUE HOSPITAL,
DR. I. O. WOODRUFF, DIRECTOR

PARATHYROID INSUFFICIENCY TREATED WITH DIHYDROTACHYSTEROL (A-T 10)

PARATHYROID insufficiency is a distressing disease which fortunately is rather uncommon. It occurs in two forms: (1) so-called *idiopathic* hypoparathyroidism, and (2) *postoperative* parathyroid insufficiency. The former is rare and the latter follows operations on the thyroid gland in about 1.5 per cent of thyroidectomies. Some of these cases of postoperative hypoparathyroidism are temporary, being due to a disturbance in the blood supply or to trauma to the parathyroids in removing the overlying thyroid tissue. Occasionally the parathyroids are permanently injured at the time of operation; or, not being recognized, they may even be removed along with the thyroid gland. In such cases the parathyroid insufficiency is permanent and the symptoms are severe. These patients are difficult to treat and require a type of therapy which can be continued for years. So far, implantation of parathyroid tissue has not been a lasting answer to the problem. It is to be hoped that, eventually, it will be possible to transplant glandular material. In the meantime we are forced to rely on substitution therapy and various drugs.

Clinical Picture.—The clinical picture of postoperative parathyroid insufficiency is readily recognized: shortly after thyroidectomy the patient complains of stiffness in the muscles of the extremities with numbness and tingling in the fingers. The muscles of the face may feel stiff and the voice may become hoarse. The hands may develop carpopedal spasm, the breathing tends to be stertorous, and later actual convulsive seizures may take place. These are tonic in nature and leave the pa-

tient with sore muscles and general weakness. The patient sometimes is unconscious with these attacks, simulating epilepsy. A blood calcium taken at this time will show a low figure. Intravenous injection of calcium will stop the tetany promptly.

Treatment.—Therapy is directed at raising the blood calcium level. This may be done in a number of ways: The *immediate* treatment of tetany is intravenous calcium, usually in the form of 10 per cent calcium gluconate, 10 or 20 cc. administered slowly. The tetany is temporarily relieved by this method, only to return within a day if other measures are not taken to maintain the blood calcium level. For cases of *transient tetany* following thyroid operations, intravenous calcium given daily may be continued for a number of days or parathormone may be tried. Both of these methods are not suited to prolonged use; the former because it entails one or more daily intravenous injections, the latter also because of the need of hypodermic injections and furthermore because the patient soon develops a resistance to the hormone which renders it less and less effective.

Until recently patients with *chronic* tetany have been treated by large doses of calcium by mouth, supplemented with vitamin D concentrate to increase the calcium absorption in the intestine and to raise the blood calcium level. Calcium lactate, 25 gm. daily, and large doses of viosterol, have been recommended. In spite of these, some patients have not been helped. Low phosphorus diets have been tried, and this likewise has not met with success in all cases.

The treatment of parathyroid insufficiency has therefore been discouraging until the recent addition of *dihydrotachysterol* (A-T 10) to our list of specific medications. A-T 10 was first introduced in the treatment of hypoparathyroid tetany in 1933 by Holtz in Germany. Since then numerous papers have confirmed his observations, most of the early reports being in the German literature. More recently A-T 10 has become available in the United States through importation. A recent communication from the agent assures an ample supply.

Chemically, *A-T 10* is a derivative of irradiated ergosterin. The fraction, tachysterin, is converted to dihydrotachysterol to

make it suitable for administration by mouth. Its abbreviation to "A-T 10" stands for "anti-rachitic preparation No. 10."

The *action* of the drug has been thoroughly investigated by Dr. Albright and his associates in Boston. They studied its physiologic activity and compared its action with that of vitamin D and parathormone in the treatment of hypoparathyroidism and resistant rickets. It is concluded that vitamin D and A-T 10 increase the calcium absorption from the intestine and increase phosphorus excretion in the urine, the A-T 10 having more effect on the phosphorus excretion than vitamin D. The action of A-T 10 is more rapid than vitamin D, but not as prompt as parathormone in raising the blood calcium. The effect of A-T 10 is more prolonged than parathormone. Dihydrotachysterol is said to have no anti-rachitic action. A-T 10 would therefore appear to be an ideal drug for the treatment of parathyroid insufficiency.

The *dosage* of A-T 10 varies with the individual and the severity of the condition. Its action is cumulative and prolonged. Ten cubic centimeters daily may be given for a week or two and, with symptomatic improvement, the dose is diminished. One half to one cc. daily usually is sufficient to maintain most patients. During administration it is important to take frequent *blood calcium determinations* as this drug is very potent and may raise the calcium above normal, in which case the patient may complain of lassitude, headache, loss of appetite and nausea with vomiting. A-T 10 is expensive and, in treatment, as in the case to be presented, we could not afford to begin with large initial doses. We therefore gave the maintenance dose of 1 cc. a day, supplementing this with calcium lactate by mouth and viosterol. Experimental data show the rationale for this method of treatment. Calcium by mouth provides available calcium for absorption, reducing any possible tendency to mobilize calcium from the bones. The viosterol is effective in increasing the absorption of calcium from the intestine and therefore adds to the efficiency of A-T 10. Furthermore, viosterol has a prolonged action and theoretically would tend to keep the blood calcium at a more constant level. The following case will serve to illustrate the points just discussed:

tient with sore muscles and general weakness. The patient sometimes is unconscious with these attacks, simulating epilepsy. A blood calcium taken at this time will show a low figure. Intravenous injection of calcium will stop the tetany promptly.

Treatment.—Therapy is directed at raising the blood calcium level. This may be done in a number of ways: The *immediate* treatment of tetany is intravenous calcium, usually in the form of 10 per cent calcium gluconate, 10 or 20 cc. administered slowly. The tetany is temporarily relieved by this method, only to return within a day if other measures are not taken to maintain the blood calcium level. For cases of *transient tetany* following thyroid operations, intravenous calcium given daily may be continued for a number of days or parathormone may be tried. Both of these methods are not suited to prolonged use; the former because it entails one or more daily intravenous injections, the latter also because of the need of hypodermic injections and furthermore because the patient soon develops a resistance to the hormone which renders it less and less effective.

Until recently patients with *chronic* tetany have been treated by large doses of calcium by mouth, supplemented with vitamin D concentrate to increase the calcium absorption in the intestine and to raise the blood calcium level. Calcium lactate, 25 gm. daily, and large doses of viosterol, have been recommended. In spite of these, some patients have not been helped. Low phosphorus diets have been tried, and this likewise has not met with success in all cases.

The treatment of parathyroid insufficiency has therefore been discouraging until the recent addition of *dihydrotachysterol* (A-T 10) to our list of specific medications. A-T 10 was first introduced in the treatment of hypoparathyroid tetany in 1933 by Holtz in Germany. Since then numerous papers have confirmed his observations, most of the early reports being in the German literature. More recently A-T 10 has become available in the United States through importation. A recent communication from the agent assures an ample supply.

Chemically, *A-T 10* is a derivative of irradiated ergosterin. The fraction, tachysterin, is converted to dihydrotachysterol to

make it suitable for administration by mouth. Its abbreviation to "A-T 10" stands for "anti-rachitic preparation No. 10."

The *action* of the drug has been thoroughly investigated by Dr. Albright and his associates in Boston. They studied its physiologic activity and compared its action with that of vitamin D and parathormone in the treatment of hypoparathyroidism and resistant rickets. It is concluded that vitamin D and A-T 10 increase the calcium absorption from the intestine and increase phosphorus excretion in the urine, the A-T 10 having more effect on the phosphorus excretion than vitamin D. The action of A-T 10 is more rapid than vitamin D, but not as prompt as parathormone in raising the blood calcium. The effect of A-T 10 is more prolonged than parathormone. Dihydrotachysterol is said to have no anti-rachitic action. A-T 10 would therefore appear to be an ideal drug for the treatment of parathyroid insufficiency.

The *dosage* of A-T 10 varies with the individual and the severity of the condition. Its action is cumulative and prolonged. Ten cubic centimeters daily may be given for a week or two and, with symptomatic improvement, the dose is diminished. One half to one cc. daily usually is sufficient to maintain most patients. During administration it is important to take frequent *blood calcium determinations* as this drug is very potent and may raise the calcium above normal, in which case the patient may complain of lassitude, headache, loss of appetite and nausea with vomiting. A-T 10 is expensive and, in treatment, as in the case to be presented, we could not afford to begin with large initial doses. We therefore gave the maintenance dose of 1 cc. a day, supplementing this with calcium lactate by mouth and viosterol. Experimental data show the rationale for this method of treatment. Calcium by mouth provides available calcium for absorption, reducing any possible tendency to mobilize calcium from the bones. The viosterol is effective in increasing the absorption of calcium from the intestine and therefore adds to the efficiency of A-T 10. Furthermore, viosterol has a prolonged action and theoretically would tend to keep the blood calcium at a more constant level. The following case will serve to illustrate the points just discussed:

tient with sore muscles and general weakness. The
sometimes is unconscious with these attacks, simulati
lepsy. A blood calcium taken at this time will shov.
figure. Intravenous injection of calcium will stop the
promptly.

Treatment.—Therapy is directed at raising the
calcium level. This may be done in a number of way
immediate treatment of tetany is intravenous calcium,
in the form of 10 per cent calcium gluconate, 10 or 20
ministered slowly. The tetany is temporarily relieved
method, only to return within a day if other measures :
taken to maintain the blood calcium level. For cases o
sient tetany following thyroid operations, intravenous c
given daily may be continued for a number of days or
thormone may be tried. Both of these methods are not
to prolonged use; the former because it entails one or
daily intravenous injections, the latter also because of th
of hypodermic injections and furthermore because the
soon develops a resistance to the hormone which renders
and less effective.

Until recently patients with *chronic* tetany have
treated by large doses of calcium by mouth, supplemente
vitamin D concentrate to increase the calcium absorption
intestine and to raise the blood calcium level. Calcium lt
25 gm. daily, and large doses of viosterol, have been r
mended. In spite of these, some patients have not been h
Low phosphorus diets have been tried, and this likewis
not met with success in all cases.

The treatment of parathyroid insufficiency has the:
been discouraging until the recent addition of *dihydrot
sterol* (A-T 10) to our list of specific medications. A-
was first introduced in the treatment of hypoparathyroid t
in 1933 by Holtz in Germany. Since then numerous p
have confirmed his observations, most of the early repor:
ing in the German literature. More recently A-T 10 ha.
come available in the United States through import:
A recent communication from the agent assures an a
supply.

Chemically, *A-T 10* is a derivative of irradiated ergos:
The fraction, tachysterin, is converted to dihydrotachyster

make it suitable for administration by mouth. Its abbreviation to "A-T 10" stands for "anti-rachitic preparation No. 10."

The *action* of the drug has been thoroughly investigated by Dr. Albright and his associates in Boston. They studied its physiologic activity and compared its action with that of vitamin D and parathormone in the treatment of hypoparathyroidism and resistant rickets. It is concluded that vitamin D and A-T 10 increase the calcium absorption from the intestine and increase phosphorus excretion in the urine, the A-T 10 having more effect on the phosphorus excretion than vitamin D. The action of A-T 10 is more rapid than vitamin D, but not as prompt as parathormone in raising the blood calcium. The effect of A-T 10 is more prolonged than parathormone. Dihydrotachysterol is said to have no anti-rachitic action. A-T 10 would therefore appear to be an ideal drug for the treatment of parathyroid insufficiency.

The *dosage* of A-T 10 varies with the individual and the severity of the condition. Its action is cumulative and prolonged. Ten cubic centimeters daily may be given for a week or two and, with symptomatic improvement, the dose is diminished. One half to one cc. daily usually is sufficient to maintain most patients. During administration it is important to take frequent *blood calcium determinations* as this drug is very potent and may raise the calcium above normal, in which case the patient may complain of lassitude, headache, loss of appetite and nausea with vomiting. A-T 10 is expensive and, in treatment, as in the case to be presented, we could not afford to begin with large initial doses. We therefore gave the maintenance dose of 1 cc. a day, supplementing this with calcium lactate by mouth and viosterol. Experimental data show the rationale for this method of treatment. Calcium by mouth provides available calcium for absorption, reducing any possible tendency to mobilize calcium from the bones. The viosterol is effective in increasing the absorption of calcium from the intestine and therefore adds to the efficiency of A-T 10. Furthermore, viosterol has a prolonged action and theoretically would tend to keep the blood calcium at a more constant level. The following case will serve to illustrate the points just discussed:

Illustrative Case.—B. M., a fifteen-year-old school girl, first came to Bellevue Hospital in March, 1931, and was admitted to the First Surgical Division. At that time she was complaining of enlargement of the thyroid gland of four months' duration associated with a choking sensation and difficulty in swallowing. She had noticed palpitation, dyspnea on exertion, tremor and sweating of the hands. She had lost weight. The record of her BMR in the clinic is not available, but after a few days in the hospital on Lugol's solution, her BMR was plus 16 per cent. On physical examination she was a fairly well developed and nourished, nervous girl weighing 114 pounds. Her temperature was 100° F. (po) and her pulse 120. She had slight exophthalmos and lid lag, an enlarged nodular thyroid, overactive heart and fine tremor of hands. After the usual preparation, a subtotal thyroidectomy was performed. The pathologist reported toxic adenomas in both lobes. The patient had an infection of the wound, but this cleared up in a week without complication.

The patient improved for a few months, but during the same year she again noted a gradual return of the lump in her neck. She was readmitted to the hospital in January, 1934, with a recurrence of her old complaints. In addition, she was more nervous and her eyes had become more prominent. She had lost 7 pounds in the previous two months; her weight was 141 pounds. The BMR was plus 25 per cent. Physical examination at this time showed the classical findings of hyperthyroidism. Partial thyroidectomy was again undertaken. Her postoperative course was smooth and she was discharged improved.

The patient then married and in 1936 was delivered of a normal girl without difficulty. In spite of taking iodine intermittently she came back to the hospital in January, 1937, with a four months' history of nervousness, crying spells, palpitation and dyspnea. Although her appetite had increased, she had lost 45 pounds in the ten months. A nodule was palpable in the left lobe of the thyroid. It was noted that the patient was hoarse. An E.N.T. consultant reported very little motion in the vocal cords. A BMR at this time was plus 3.7 per cent (while on iodine therapy). At the third operation the pyramidal lobe was removed and part of the left lobe, leaving behind about one fifth of the thyroid tissue on this side. Pathologically the gland again showed the same picture of toxic adenoma. No parathyroid tissue was noted grossly and the sections revealed none.

Two days postoperatively the patient complained of stiffness in the fingers and muscle cramps. A positive Chvostek sign was found to be present. She received 10 cc. of calcium gluconate (10 per cent) intravenously twice daily. In spite of this, carpopedal spasm appeared and the Chvostek sign persisted. On the sixteenth day she was sent to a convalescent home, where she was able to remain for only two days because of tetany. On readmission the patient stayed in the hospital for over a month, during which time she received all the usual forms of treatment of tetany, including high calcium, low phosphorus and ketogenic diets; calcium by mouth and intravenously; viosterol and parathormone. She was finally discharged, still having tetany, and was instructed to return to the clinic daily for intravenous calcium.

Her progress having been unsatisfactory after a month, she was sent to the First Medical Service. The day after admission she had a convulsive seizure, for which she received calcium gluconate intravenously. Physical ex-

amination at this time showed a rather thin twenty-one-year-old girl with slight exophthalmos and lid lag. There were no other signs of hyperthyroidism. There was hoarseness of the voice due to right recurrent laryngeal paralysis. Carpopedal spasm was present and the Chvostek and Trousseau signs were easily elicited. The urine and blood Wassermann were negative. x-Rays of the skeleton showed no decalcification of the bones. The patient was placed on a low phosphorus diet, viosterol (10 drops t.i.d.) and 30 gm. of calcium lactate o.d. After ten days it was possible to discharge her. She was slightly improved. In the clinic she continued to receive viosterol, calcium lactate and intravenous calcium when necessary.

In April, 1937, four months after her last operation, a blood partition through the courtesy of Dr. Gutman at the Presbyterian Hospital was as follows: Calcium, 5.7 mg. per cent; inorganic phosphorus, 5.5 mg. per cent; serum phosphatase, 3.1 Bodansky units; N. P. N., 28 mg. per cent; total protein, 8; albumin, 4.8; globulin, 3.2; euglobulin, 0.7.

One year ago this patient returned to the Endocrine Clinic. She had suffered several severe convulsions, with loss of consciousness for a period of ten to fifteen minutes and biting of her tongue. Her breathing was stertorous and her voice very hoarse. Chvostek and Trousseau's signs were positive. Carpopedal spasm was present, and there was a marked brownish scaling of the dorsum of the hands, not unlike mild pellagra in appearance. Her blood pressure was 120/80. She had lost 12 pounds in six months, weighing 110 pounds. The blood calcium was 4.8; phosphorus, 5.8.

This patient had gone one year and ten months in a profound degree of parathyroid insufficiency, unrelieved by the customary forms of therapy. At this point A-T 10 was started, the patient being instructed to take 1 cc. o.d. She was told to continue to take 2 teaspoonfuls of calcium lactate and 20 drops of viosterol daily. One week later she reported that she felt better. Chvostek sign was still present. Two weeks after commencing A-T 10 she had gained 2 pounds and felt much improved. The skin lesion had disappeared. Next week she put on another 1½ pounds, but had stopped taking the medicine owing to a domestic disturbance. She was urged to resume the A-T 10. Toward the last of November, she had no complaints, weighed 114½ pounds. Chvostek and Trousseau's signs were not present. In December, a blood calcium was 7 per cent. In April of this year she weighed 115½ pounds and had no symptoms or signs of hypoparathyroidism.

The blood chemistry at this time showed: calcium, 9.9; phosphorus, 4.6; N. P. N., 33, and phosphatase, 0.9. The blood calcium had reached a normal level. We now stopped the A-T 10, hoping that we might maintain the level by giving only calcium lactate and viosterol. She reported a month and a half later some tingling and numbness of the hands. Two months after stopping the A-T 10, the Chvostek returned on the right side. The blood calcium had fallen to 5.2 mg. per cent, and the phosphorus had risen to 5.6. A-T 10 was resumed. During the summer she did not follow directions closely, but took the medicine as she thought she needed it. She judged this by whether she could elicit the Chvostek sign herself. Of course, such a procedure kept her on the borderline of tetany. At the end of September her blood calcium was 6.2. After receiving A-T 10, 2 cc. (o.d.) for ten days, then

TABLE 1

Date	Weight		Medication					Blood chemistry						Signs	
			Ca.	Vios-terol.	Low P diet.	A–T 10		Ca.	P.	Phos-pha-tase.	NPN			Chvos-tek.	Trous-seau.
4/19/37	122	..	Gm. 25	Gtts. 30	..	cc. ..	.	5.7	5.5	3.1	28	..		+	+
3/30/38	115½	..	25	30	+	..	..	..	..	..	..	..		:	:
10/19/38	110¼	..	10	20	..	1.0	..	4.8	5.8	..	..	..		+	+
11/2/38	112	..	10	20	..	1.0	..	..	..	..	..	..		+	+
11/9/38	113½	..	10	20	..	1.0	..	..	..	..	..	..		+	0
11/23/38	114½	..	10	20	..	1.0	..	..	..	..	..	..		0	0
12/21/38	..	..	10	20	..	1.0	..	7.0	..	..	..	..		0	0
3/1/39	115½	..	10	20	..	1 0	..	9.9	4.6	0.9	33	..		0	0
4/18/39	117½	..	10	20	..	..	..	..	..	..	..	..		0	0
5/3/39	116	..	10	20	..	1.0	..	5.5	5.6	..	..	..		0	0
5/31/39	115	..	10	20	..	0.5	..	..	..	..	..	..		+	+
9/27/39	117½	..	10	10	..	2.0	..	6.2	5.4	..	..	..		+	0
10/19/39	114½	..	10	20	..	1.0	..	8.5	4.3	..	..	..		0	0

dropping back to 1 cc. (o.d.), the blood calcium was 8.5 at the end of three weeks.

It appears that this patient's maintenance dose is in the neighborhood of 1 cc. daily. A recent BMR was minus 5 per cent. The chart shows the essential data on this case (Table 1). It will be seen at the onset that the blood calcium continued to drop, even though the patient was placed on large doses of calcium lactate and viosterol. She did not respond to a low phosphorus diet. When the blood calcium was at the very low figure of 4.8 mg. per cent, dihydrotachysterol was administered. There is a gradual rise in blood calcium, and as this takes place the phosphorus falls. This is usually the case. At the point where the blood calcium was normal, the A-T 10 was stopped. The continuation of calcium and viosterol was not able to maintain a normal level and the blood calcium fell, with a return of the signs of tetany. The administration of 2 cc. of A-T 10 over a brief time caused a more rapid rise in the blood calcium than when only 1 cc. was given at the onset of this type of therapy. We plan to continue giving her 1 cc. of A-T 10 daily.*

Conclusions.—Dihydrotachysterol is a potent drug in calcium metabolism. It is particularly useful in parathyroid insufficiency, in which it is capable of relieving tetany by raising the blood calcium to normal and maintaining it at this level.

BIBLIOGRAPHY

Holtz, F.: Die Behandlung der Post-operative Tetanie. Arch. f. klin. Chir., (Proc.) **177**: 32, 1933.

Arnold, C. H., and Blum, H.: Control of Hypoparathyroidism. West. J. Surg., **44**: 546, 1936.

Swinton, N. W.: Post-operative Parathyroid Tetany. N. E. J. Medicine, **217**: 165, 1937.

Albright, Fuller, Bloomberg, Ester, Drake, Truman, and Sulkowitch, Hirsch W.: Comparison of the Effects of A-T 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypothyroidism. J. of Clin. Invest., **17**: 317, May, 1938.

Albright, Fuller, Sulkowitch, Hirsch W., and Bloomberg. Ester: A Comparison of the Effects of Vitamin D, Dihydrotachysterol (A-T 10), and Parathyroid Extract on the Disordered Metabolism of Rickets. J. of Clin. Invest., **18**: 165, Jan., 1939.

MacBryde, Cyril: The Treatment of Parathyroid Tetany with Dihydrotachysterol. J.A.M.A., **111**: 304, July 23, 1938.

* Since this paper was submitted for publication the patient has become pregnant. There are few such cases in the literature and it is stated that during pregnancy much larger doses of A-T 10 are required. This patient is now in her ninth month of pregnancy and is progressing normally. During the first five months she received 1 cc. of A-T 10 daily. The dose was increased to 3 cc. daily for the last four months. Her blood calcium level has been maintained between 9.1 and 9.8 mg. per cent through this period.

Margolis, H. M., and Krame, Gilbert: Post-operative Parathyroid Tetany. J.A.M.A., **112**: 131, March 25, 1939.

Hurxthal, Lewis M., and Claiborne, T. Sterling: The Treatment of Tetany with Dihydrotachysterol (A-T 10). N. E. J. Medicine, **220**: 911, July 1, 1939.

Rose, Edward, and Sunderman, F. William: Effect of Dihydrotachysterol in Treatment of Parathyroid Deficiency. Arch. of Int. Med., **64**: 217, Aug., 1939.

CLINIC OF DR. W. P. THOMPSON AND CATHERINE A. ILLYNE, B.A.

DEPARTMENT OF MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE PRESBYTERIAN HOSPITAL

THE CLINICAL AND HEMATOLOGIC PICTURE RESULTING FROM BONE MARROW REPLACEMENT

REPLACEMENT of bone marrow by foreign tissue as a cause of anemia has been recognized for many years. The clinical picture which results from this condition has been given a variety of names: *myelophthisic anemia, osteosclerotic anemia,* and *chronic non-leukemic myelosis.* Under the latter term, Hickling[1] has recently reviewed the literature with a careful and detailed summary of the reported cases, including seven of his own.

Clinical recognition of this syndrome is important, as the two forms of therapy usually advised, radiotherapy to the spleen and splenectomy, are *contraindicated* once the nature of the disturbance is understood.

During the past few years the Combined Spleen Clinic of the Presbyterian Hospital has had the opportunity of studying thirteen of these cases. This study has shown that replacement of the marrow results in a uniform clinical and hematologic pattern, a pattern that is recognizable before operation and before death.

These patients present the *symptoms* of anemia and, frequently, purpura. The spleen enlarges sometimes to enormous size. There is severe anemia with evidence of regeneration and there is a normal or moderately elevated leukocyte count with the differential count showing the presence of immature red and white cells. The platelets are markedly reduced. The only significant variable in this disease pattern is the velocity

of the progress of the disturbance, and this varies enormously. If the marrow replacement is due to a highly malignant infiltrating carcinoma, the progress of the disease is necessarily rapid. If, on the other hand, the bone marrow is being replaced by slowly developing connective tissue, a prolonged and relatively benign course is observed:

Case I (J. P., No. 432501, Autopsy No. 12,262).—This patient was an Italian woodworker of twenty-nine who was admitted to the Medical Service of the Presbyterian Hospital on October 24, 1935, with a history of increasing weakness and pallor for five weeks. There had been no previous illnesses of significance. His dietary background appeared adequate and careful study of a Department of Labor investigator revealed no industrial hazards in his work. On admission he appeared pale and chronically ill. There were no significant physical findings. The spleen could not be felt. His blood count on October 28, 1935, was: Hgb. 45 per cent; RBC 2,000,000; WBC 7,300; platelets, 68,000; reticulocytes 14.6 per cent; neutrophils 64 (1–15–48); eosinophils 2; basophils 2; myelocytes 5; lymphocytes 18, monocytes, 9; nucleated red cells 5/100. RBC fragility: Hemolysis began, Pt. .425. Cont. .425, hemolysis complete, Pt. .30, Cont. .30. The red cells showed marked anisocytosis, moderate poikilocytosis and polychromatophilia. The blood Wassermann was negative. The urine was normal. There was no evidence of jaundice. After histamine the gastric juice contained no free hydrochloric acid.

A definite clinical diagnosis was not made. Because of the severe disturbance in the bone marrow and the slight splenic enlargement which soon appeared, it was thought that the patient might have early leukemia. Many consultants were called in, many laboratory procedures were done, and after one month in the hospital it was possible only to say that his blood-forming apparatus was severely disturbed. The only clue was furnished in a note by Dr. Golden, Professor of Roentgenology, dated October 30th: "Stereoscopic films of the dorsal spine in the a.p. position and flat lateral views show no evidence of bone destruction. The intervertebral discs between 7 and 8 and 8 and 9 seem a little narrower at this level. The architecture of the vertebral bodies seems rather peculiar. The bones have a ground-glass appearance which does not seem normal, but I do not know how to interpret it. There is no evidence of bone destruction and nothing is present which can be interpreted with certainty as evidence of arthritis." x-Rays of the remainder of the skeleton, taken because of the remote possibility of osteosclerosis revealed no similar change. No Bence-Jones protein appeared in the urine, the plasma proteins were normal. On October 31 the blood count revealed: Hgb. 30 per cent; RBC 1,500,000; WBC 8,900; platelets, 63,000; reticulocytes 17.3 per cent; neutrophils 69 per cent (6–19–44); eosinophils 1 per cent; basophils 3 per cent; myelocytes 4 per cent; myeloblasts 1 per cent; lymphocytes 19 per cent; monocytes 3 per cent; normoblasts 13/100 WBC. Following one 500 cc. transfusion on November 2, unexpected improvement began. During the next three weeks the patient's weakness disappeared, his appetite returned, and his blood count rapidly returned to normal levels. He was discharged from

the hospital on November 23 and was followed at regular intervals in the clinic for the next eleven months. During this period he felt entirely well and his blood count, taken regularly, remained normal.

In October, 1936, the patient returned to the clinic complaining of his original sensation of weakness and pallor was noticed. He was readmitted to the medical ward on October 22, 1936, obviously seriously ill. The only abnormal physical findings were moderate general glandular enlargement and the spleen remained palpably enlarged. On October 23, the blood count showed Hgb. 45 per cent; RBC 2,000,000; WBC 9,300; platelets 88,000; reticulocytes 33.5 per cent; neutrophils 84 per cent (0–6–78); eosinophils 4 per cent; basophils 2 per cent; myelocytes 3 per cent; lymphocytes 25 per cent and monocytes 5 per cent. There were many normoblasts.

Because of the previous suspicion that osteosclerosis might be responsible for this man's illness, further x-ray studies of the spine were taken. These showed: "a remarkable change to have supervened since the last examination; i. e., there has developed a diffuse condensation of bone throughout the spinal segments and in the adjacent portions of both innominate bones. The condensation is markedly homogeneous. In this regard, it is unlike an osteoblastic metastasis, although this should be considered in the differential diagnosis. So-called 'marble bones' is out of the question because the lesion has developed since last year. A chemical poisoning seems unlikely from his history, although poisoning from fluorine should be considered as a possibility. Lymphosarcoma or Hodgkin's disease can give an osteoblastic picture and seems most likely in this case." Three days after admission the patient unexpectedly developed convulsive seizures, syncope and sweating. On October 27, in the early morning he became very short of breath and apprehensive. An hour later he stopped breathing.

At the time of death it was felt that the patient must have an extensive bone marrow disease. The fundamental nature of this disturbance was quite unknown and no reason for the widespread condensation of bone had been agreed upon and there was no reasonable explanation for the twelve-month remission.

At autopsy, the changes in the bones were extensively studied. All showed uniform great density. The bodies of the vertebra were very hard and little bone marrow was visible. The same was true of the femur where the medullary canal was encroached upon by a wide ivory-hard cortex, the canal being largely filled with heavy trabeculated bone. Similar changes were found in the other bones. The spleen weighed 300 gm.

"The cause of these changes was entirely obscure until the microscopic examination of the tissue uncovered the presence of an adenocarcinoma, metastasizing through the lymphatics of the lung, the thoracic and abdominal lymph nodes and the marrow of the affected bones. In the absence of any other obvious cause it seems safe to assume that the osteosclerosis is a reaction to the invading tumor. In spite of careful search, the primary site of the growth remains undiscovered. A hint as to a possible origin from the alimentary epithelium is given by the production of mucin and a cuticular border."=

The anatomic diagnosis was recorded as follows: (1) Carcinoma of un-

known origin; (2) secondary carcinoma in lymph nodes (mesenteric, abdominal, gastric, tracheobronchial, inguinal and axillary) and in diaphragm, lungs and skeleton; (3) osteosclerotic anemia; (4) extramedullary hematopoiesis in liver and spleen.

This type of tumor with its extensive infiltrating character was quite similar to the tumors described by Jarcho.[3]

Case II (G. K., No. 346900, Autopsy No. 11,963).—The patient was a sixty-five-year-old married electrician who was admitted to the medical ward on September 13, 1935, with a history of hematuria, hemoptyses and purpura for one week. There was no family history of bleeding, his diet had been adequate, and there had been no previous purpuric manifestations and no chemical exposures. Examination revealed a wasted, chronically ill, elderly man. There were several large ecchymoses and many petechiae scattered over the skin. There was no enlargement of the spleen or superficial lymph nodes at the time of admission. Physical examination was otherwise negative except for moderate prostatic hypertrophy, considered benign. A representative blood count appears in the accompanying table. Clinically he was considered to have thrombocytopenic purpura, but all who saw him felt this diagnosis was unsatisfactory in a man of this age. The blood Wassermann was negative. His urine contained many red blood cells.

During the next month, the bleeding continued, the capillary resistance dropping from 30 mm. negative pressure to 10 mm. The weakness increased. Several transfusions failed to effect the tendency to easy bleeding. x-Ray of the long bones showed no evidence of metastatic neoplasm. Various diagnostic possibilities were considered, including leukemia and metastatic carcinoma, but nothing to support these could be developed. A sternal puncture

										REPRESENTATIVE BLOOD COUNTS						
CASE	NAME	AGE	SEX	DURATION OF DISEASE	PRESENTING SYMPTOMS	R.B.C. MILLIONS	HGB % IN GMS.	W.B.C. THOUSANDS	NEUTROPHILES			LYMPHOCYTE %	MYELOBLAST %	MONOCYTE %	LYMPHOCYTE %
									JUVENILE %	STABS %	ADULT %				
1	J.P.	29	M	1 YEAR	ANEMIA	2.1	48	281	1	8	65	1	0	8	15
2	G.K.	65	M	1 MTHS.	PURPURA	3.7	73	8.0	0	6	62	1	0	0	29
3	T.G.	43	M	2 WEEKS	"	2.1	44	90	2	8	67	4	0	3	15
4	R.B.	37	F	3 MTHS.	.	2.4	47	70		50		8	0	7	42
5	F.B.	67	M	5 WEEKS	"	3.4	60	142	5	33	42	13	2	2	2
6	L.G.	32	M	5 WEEKS	"	2.6	48	356	3	23	37	12	0	2	23
7	C.T.	48	M	8 YEARS	"	3.0	54	55	1	48	24	3	2	5	14
8	A.B.	37	M	18 MTHS.	ANEMIA	2.4	40	33	3	21	50	8	2	0	11
9	W.K.	36	F	8 YEARS	.	3.3	60	140		67		15	5	8	12
10	S.F.	30	M	8 YEARS	WEAKNESS	2.8	57	208	2	20	53	3	5	0	15
11	L.K.	40	F	1 YEAR	ANEMIA	3.0	50	313	0	9	7	9	33	0	10
12	L.K.	64	F	1½ YEARS	"	2.0	50	262	4	24	30	11	1	4	24
13	B.K.	65	F	2½ YEARS	"	2.8	47	122	2	17	61	4	0	0	11

Fig. 108.—Representative

was considered, but it was decided that his great tendency to bleeding and his general weakness did not justify this procedure. On November 10, he became comatose and died. The final clinical diagnosis was: thrombocytopenic purpura, etiology unknown.

At autopsy it was found that his prostate contained a carcinoma. This had metastasized widely, as in the previous case, resulting in an extensive replacement of bone marrow in all the bones examined. Tumors were found, in addition, in many branches of the pulmonary artery and in many lymphatics. Hemorrhages were present in the brain and elsewhere. The spleen was small but contained extramedullary blood formation. Again the character of the metastases was similar to that described by Jarcho as "diffusely infiltrating carcinoma." The final anatomic diagnosis was: (1) carcinoma of the prostate; (2) secondary carcinoma of bone (vertebrae, ribs and lungs); (3) thrombocytopenic purpura—clinical; (4) hemorrhages in brain (cerebellum and fourth ventricle), meninges. lungs. skin, kidney pelves, and (5) extramedullary blood formation—spleen and liver.

Case III (T. G., No. 531696, Autopsy No. 12,744).—A forty-five-year-old white male was admitted to the medical ward with a brief complaint of epigastric pain, vomiting and loss of weight. At the time of admission he was suffering from a severe nose bleed and moderate fever. The clinical course was rapidly progressive with purpura as the outstanding physical finding. The spleen was slightly enlarged. Gastro-intestinal x-rays revealed an ulcer on the lesser curvature of the stomach. The blood count appears on the chart (Fig. 108). There was a shift to the left in the neutrophils and myelocytes were seen. Normoblasts were present approximately one for every 100 white cells. The platelets numbered 46,000. The patient died shortly after admission without a definite diagnosis.

At autopsy, near the base of the gastric ulcer was found a small area of gastric carcinoma. This carcinoma had widely infiltrated the long bones and

No.	Anatomic No.	Reticulocytes %	Normoblasts per 100 W.B.C.	Platelets thousands	Purpura	Splenomegaly	Path +	Blood formation in spleen	Infiltration of bone marrow			Site of primary tumor
									Tumor	Connective tissue	Bone	
1	1	333	9	48	++	+	12,242	+++	+++	-	+++	UNKNOWN
4	0	-	1	35	+++	0	11,943	++	+++	-	++	PROSTATE
4	0	33	1	48	+++	0	12,744	++	+++	-	++	STOMACH
0	4	-	OCCASIONAL	REDUCED	+++	0	10,334	+	+++	++	-	COLON
2	2	-	3	31	+++	+	12,48	+++	+++	++	++	PROSTATE
0	0	22	18	33	+++	+	12,329	+	+++	-	-	STOMACH
0	0	53	1	13	++	++	13,584 W.P. 2,89	+++	-	+++	++	STERNAL MARROW FIBROTIC AND INACTIVE
1	4	45	9	33	+	+++	W.P. 3,290 3,291	+++	-	++	++	MARROW CONTAINS NEW BONE CONNECTIVE TISSUE AND MEGAKARYOCYTES
0	0	-	OCCASIONAL	REDUCED	+	+++	11,91	+++	-	+++	+++	MARROW REPLACED BY CONNECTIVE TISSUE AND BONE
0	0	45	10	ANTE OR ABOVE HIGH SPACE	+	+++	SP. 4,184 W.P 3,437	+++	-	-	+++	STERNAL MARROW FILLED WITH MEGAKARYOCYTES
3	34	83	3	600	++	+++	12,93	+++	-	+	+++	BONE AND CONNECTIVE TISSUE POCKETS MEGAKARYOCYTES, TISSUE, MANY EOSINOPHILS
0	0	43	7	87	+	++	W.P.3,932	-	-	++	++	MARROW REPLACED BY CONNECTIVE TISSUE
1	2	33	18	85	0	++	W.P 3,844	-	-	++	++	STERNAL MARROW REPLACED BY CONNECTIVE TISSUE

blood counts.

there were metastases of the liver and of the lungs. Histologically, the picture in the bone marrow was similar to the previous cases. The spleen weighed 220 gm. and contained scattered areas of blood formation.

Case IV (R. B., No. 230193, Autopsy No. 10,356).—A thirty-seven-year-old white female came into the hospital with a three-year history of intermittent pains in the back, legs, and epigastrium. These symptoms were never particularly severe and there had been no significant relationships. At the time of admission she was pale and obviously ill. There were many purpuric spots on the extremities. There was a firm mass in the epigastrium. The spleen was not palpably enlarged. The disease progressed rapidly with increasing anemia and purpura. At the time of the patient's death, it was felt that she almost surely had carcinoma with widespread metastases. This diagnosis was confirmed at autopsy, at which time the primary site was found to be in the large intestine, and again the bone marrow was almost entirely replaced by the infiltrating type of metastases. In addition there was a proliferation of connective tissue in the marrow of various bones. The spleen weighed 180 mg. and contained areas of erythropoiesis. A representative blood count appears in Fig. 108.

Case V (F. B., No. 48537, Autopsy No. 13,146).—A white male of sixty-seven entered the hospital with a five weeks' history of pain in the hip and shoulder, ecchymosis and other purpuric manifestations, and one hematemesis shortly before the time of admission. On examination he was found to be pale. There were many petechial spots and subcutaneous hemorrhages. The spleen was not enlarged. The blood showed RBC 3,400,000; Hgb. 60 per cent; WBC 16,200; 62 per cent neutrophils, 17 per cent myelocytes, with again a marked shift to the left. The platelets numbered 31,000. Frequent nucleated red cells were seen. A clinical diagnosis of carcinoma of the prostate with multiple metastases to the bones was made after study. This diagnosis was confirmed at autopsy, where again the bone marrow was found replaced wherever examined by neoplastic cells. The spleen weighed 300 gm. and showed many areas of blood formation.

Case VI (L. G., No. 506271, Autopsy No. 12,328).—A white male of thirty-two came to the hospital with a history of weakness, pallor and bleeding from the gums for the past five weeks. Hematuria and melena appeared shortly before admission. On examination he appeared pale and acutely ill. There was a high swinging fever, his gums were bleeding, purpuric spots appeared, his urine contained numerous erythrocytes and his stool guaiac was positive. The spleen was palpably enlarged and an indefinite epigastric mass was noted. The blood showed RBC 2,600,000; Hgb. 48 per cent; WBC 20,-000; 63 per cent neutrophils with marked left shift, and 12 per cent myelocytes. The platelets fell to 30,000 and numerous nucleated red cells were seen. A clinical diagnosis of lymphoblastoma was made. Autopsy revealed a carcinoma of the stomach with extensive, widespread metastases. The marrow of the ribs and vertebrae was almost entirely replaced by tumor. The spleen weighed 300 gm. and contained tumor cells as well as areas of blood formation.

The six preceding cases represent the rapid, fulminating picture that occurs when the bone marrow is being invaded by malignant tumor. It will be noticed that *progressive anemia* was present in all and that this anemia was associated with the presence of normoblasts in the peripheral blood. In all, purpura with thrombocytopenia was a presenting symptom. In all there was a left shift in the neutrophils.

The following cases are examples of the same type of response, with greatly reduced velocity, and a relatively benign course which is associated with marrow replacement by fibrous tissue rather than neoplasm.

Case VII (C. T., No. 430794).—An Italian male presents a most involved and prolonged history. Over a period of several years this patient complained of mild to moderate purpuric manifestations and, shortly before he was seen in this hospital, pallor appeared. He was seen by many physicians who found a moderate degree of anemia, a normal total white count with definite shift to the left, and very low platelet levels. In addition, there was moderate enlargement of the spleen. No definite clinical diagnosis was made during the first years of this illness, but it was suspected that he might have idiopathic thrombocytopenic purpura and, for this reason, he was referred to this hospital for splenectomy. Splenectomy was performed on October 30, 1934, by Dr. A. O. Whipple. The patient made a satisfactory postoperative recovery and was discharged without any apparent improvement. The spleen weighed 540 gm. Histologically it showed widespread extramedullary blood formation with many islands of megakaryocytes. During the four years following splenectomy, the patient was observed frequently.

Because of the histologic findings in the spleen and the persistently abnormal blood counts, it was felt that osteosclerotic anemia was a likely diagnosis, although x-rays of the long bones showed no particular change. Sternal marrow biopsy was therefore performed and this showed that the normal marrow had been almost entirely replaced by strands of connective tissue. A few fat cells remained and an occasional primitive blood cell could be found. After four years of repeated transfusions the patient returned to Italy where he died. Autopsy was not obtained. The final clinical diagnosis was: Fibrosis of the bone marrow and osteosclerotic anemia.

Case VIII (A. B., No. 513934).—A Jewish male of thirty-seven was referred to the Spleen Clinic by his physician in Ohio for diagnosis. The patient complained of increasing weakness and pallor of one year's duration. On physical examination he was found to have an enormous spleen that descended into the pelvis and extended across the midline. He was covered with petechiae and small purpuric spots. His blood showed: RBC 2,400,000; Hgb. 40 per cent; WBC 3,300; neutrophils 74 per cent, with marked shift to the left, 8 per cent myelocytes, 2 per cent myeloblasts, reticulocytes were increased to 8 per cent, and nucleated red cells were present in large numbers. Platelets numbered 59,000. On admission it was felt that he probably was suffering

from myeloid leukemia, which was the diagnosis with which he was referred. However, the blood smear as well as the clinical course suggested to us the possibility that we might be dealing with another instance of bone marrow fibrosis. With this in mind, a sternal marrow biopsy was performed which revealed the findings of marrow fibrosis with delicate strands of connective tissue infiltrating the bone marrow in all directions. There were numerous megakaryocytes but relatively few other bone marrow elements. Splenic puncture was performed, and the splenic section revealed widespread extra-medullary blood formation with many megakaryocytes and many nucleated red cells. He was referred back to his private physician with the diagnosis of osteosclerotic anemia and splenomegaly due to extramedullary blood forma-tion. His subsequent course was progressively downhill and he died approxi-mately two years after the onset of his symptoms. No autopsy was obtained.

Case IX (M. H., No. 326709, Autopsy No. 11,318).—An American woman of forty-one had a seven-year history of mild pallor and progressive spleno-megaly. During this seven years she was seen by various physicians who felt that the diagnosis of myelocytic leukemia was likely because of the moderate anemia, the persistently elevated white count, and the presence of myelocytes and normoblasts in all smears. The platelets were markedly reduced but were never counted. On examination shortly before death, she was found to have an enormous spleen and moderate purpura. Because of the unusually long history and the absence of any clear-cut evidence of myelocytic leukemia, we were inclined to doubt that diagnosis.

At autopsy she was found to have a spleen weighing 3000 gm. Histo-logically this organ showed a marked degree of extramedullary blood forma-tion with numerous islands of megakaryocytes, suggesting leukemic infiltration. The bone marrow showed extensive fibrosis with overproduction of bone. There was a general replacement of all the normal elements by this connective tissue but rare islands of megakaryocytes remained. The final diagnosis was osteosclerotic anemia with extramedullary blood formation.

Case X (S. F., No. 226165).—An American male of twenty-nine was first seen in 1939 with a one-year history of weakness. During this year he had had occasional nose bleeds and had passed moderate amounts of blood by rectum. On examination he was found to have an enormous spleen. There was a moderate degree of anemia and the platelets were reduced. The WBC numbered 20,000 with 69 per cent neutrophils and 2 per cent myelocytes. There was a marked shift to the left and many nucleated red cells were found. Splenectomy was performed by Dr. Whipple in 1929 and a spleen weighing 1000 gm. was removed. On section this was found to show extramedullary blood formation. During the following years the patient's condition remained approximately static. On liver and iron and occasional transfusions he was able to be up and about. Because of the characteristics of the blood smears and the presence of marked extramedullary blood formation in the spleen, he was asked to return for sternal marrow biopsy. This was performed and re-vealed moderate fibrosis and, again, many islands of megakaryocytes. The patient is still living. Clinical diagnosis: Osteosclerotic anemia, with fibrosis of the bone marrow.

Case XI (L. H., No. 522385. Autopsy No. 12.765).—An American woman of forty was referred to the Spleen Clinic at the Presbyterian Hospital because of splenomegaly and weakness. Her history was vague, but for a year or more when she had noted progressive weakness, pallor and dyspnea. On examination the spleen was found to fill the entire left side of the abdomen. There were many petechiae and purpuric spots. There was a severe degree of anemia and thrombocytopenia. A representative blood count is shown in Table 1.

As this degree of basophilia had never been seen before in this clinic, we were unable to make a satisfying diagnosis. The possibility of basophilic leukemia naturally had to be considered, but the literature on this subject suggested that this was not a disease entity. A sternal marrow biopsy was performed, which showed that the marrow had been largely replaced by compact masses of cells resembling megakaryocytes. Special stains showed the specific granules of these cells. In addition, there was a marked decrease in primitive red cells and white cells and there were areas of moderate fibrosis. A tentative diagnosis of osteosclerotic anemia was made and, for this reason, splenectomy and radiotherapy were felt to be contraindicated. On liver and iron and occasional transfusions she regained considerable strength and was allowed to go to Florida for several months. When she returned it was obvious that the disease process was progressing. She was readmitted to the ward where she died shortly after.

Autopsy revealed widespread increase in the osteoid tissue of the bone marrow with some accumulations of megakaryocytes. The spleen was filled with islands of blood formation with megakaryocytes in great quantities. The final diagnosis was osteosclerotic anemia with extramedullary blood formation. This case is being published in detail by Dr. M. N. Richter elsewhere. No satisfactory explanation of the high degree of basophilia was ever found.

Case XII (L. H., No. 275805).—An American woman of fifty-eight has been followed for many years in this hospital. She was first seen in 1930 complaining of vague pains in the bones. At this time she was found to have moderate degree of polycythemia with a red count persistently over 6,000,000. During the ensuing eight years this polycythemia tended to diminish without any specific therapy, and her spleen enlarged. There was constant moderate increase in her total number of white cells, again with the marked shift to the left in the neutrophils, and there was a persistent decrease in the number of platelets. Nucleated red blood cells were visible on nearly all the blood smears. As the anemia developed it became apparent that the diagnosis of osteosclerosis had to be considered, particularly as x-rays of the long bones showed areas of marrow condensation. In 1938 a sternal marrow biopsy was performed and this showed a definite increase in osteoid tissue with replacement of the marrow by connective tissue. This patient is continuing to do well on liver and iron and occasional transfusions.

Case XIII (B. H., No. 569596).—This patient's record, strikingly similar to that in Case XII, is of an Austrian woman of sixty-five who came to this hospital in the terminal stage of a prolonged illness. For twenty years she

had had moderate splenomegaly. The first record of her disturbance appears in 1924 when she went to the Women's Hospital where a tentative diagnosis of leukemia was made. A few x-ray treatments to the spleen were given and she was lost track of. In 1927 Dr. Nathan Rosenthal saw her, at which time her spleen was enlarged, her red blood count was 6,100,000, her white cells numbered 51,000. There were 78 per cent neutrophils, 11 per cent myelocytes and 2 per cent myeloblasts. Rare nucleated red cells were seen. The platelets were normal.

At intervals for the next four years she was seen by Dr. Rosenthal who felt that she had polycythemia vera. No specific treatment was attempted. In 1931 the red count began to fall, the last count recorded in that year being 3,400,000.

Between 1931 and 1938 there were no known professional visits, but she continued to be anemic and her spleen remained enlarged.

In December, 1938, she was admitted to this hospital on the advice of her physician, Dr. Norton Brown. She was pale and exhausted. The splenomegaly continued. In addition, many of the superficial lymph nodes were enlarged. Her blood count is shown in Table 1.

Because of the duration of the illness, the splenomegaly, and the hematologic findings, it was thought she might have an osteosclerosis, the spent phase (as Dr. Rosenthal suggested) of a chronic polycythemia vera. Sternal marrow biopsy revealed an extensive replacement of the marrow by connective tissue. The lymph node removed showed changes suggestive of lymphosarcoma. She failed rapidly and died. Autopsy was refused.

In these seven cases of marrow fibrosis, an attempt has been made in all to find some agent that might be responsible for the pathologic changes. In none has there been any discernible contact with fluorine, silica, benzol, or any other chemical substance known to affect bone or bone marrow. Blood chemical studies have shown no significant abnormalities in the serum calcium, phosphorus, or phosphatase values. The fibrotic process appears to involve uniformly all the bones examined by x-ray and at autopsy; a diffuse replacement of the marrow by new bone and loose, fibrillar connective tissue with no evidence of inflammation or necrosis. Our pathologists have no explanation for this replacement and we can suggest no etiology.

Diagnosis.—A definitely visible uniformity appears when these case records are reviewed as a group, and compared with reports of similar cases in the literature.[1, 4, 5] In all of our cases the presenting clinical findings were suggestive of a "blood disease." Myelogenous leukemia was the diagnosis on admission in many while, in others, thrombocytopenic purpura was considered likely.

In all these cases there was an *anemia*, with evidence of attempted regeneration.   The anemia was severe and progressive.   The reticulocyte level was invariably high and unusual numbers of nucleated erythrocytes appeared in all instances. These nucleated red cells were largely of the normoblast type, earlier cells being relatively rare.

In all cases there was a disturbance in the *white blood cell* picture.   Although the total white count varied within wide limits, in all cases there was a neutrophilic leukocytosis accompanied by a marked shift to the left.   Myelocytes appeared in all cases; myeloblasts in most.

The *platelet level* was low in all but one case and purpura was the presenting symptom in six.

Extramedullary blood formation in the spleen is the cause of the splenomegaly, the degree of splenomegaly depending, apparently, upon the extent of marrow replacement and the duration of the disease process.

The two important differential diagnostic possibilities are the two diagnoses with which these patients are admitted to the hospital.   The first and most common diagnosis is that of *chronic myeloid leukemia*.   The reasons for this are obvious: The patients present many, sometimes almost all, of the features necessary for the establishment of this diagnosis.   They have splenic enlargement, sometimes to an enormous degree; they may or may not have an increased total white cell count; but there always are myelocytes in the peripheral blood and they present further evidence of severe bone marrow injury in the anemia and thrombocytopenia.

The *main differential points* between *bone marrow replacement* and *chronic myeloid leukemia* are these:

1. In bone marrow replacement, the total white count is sometimes low, often normal, is rarely very high, and is almost always well below the levels seen in untreated leukemia.

2. The actual number of myelocytes in the peripheral blood is rarely very high and is almost always well below the levels seen in untreated leukemia.

The important differential points between *bone marrow replacement* and *idiopathic thrombocytopenic purpura* are:

1. Idiopathic thrombocytopenic purpura, as we have seen it in over forty cases, is limited in adults to women.

2. In purpura, there is never any significant abnormality in the total or differential white blood cell count, with the possible exception of a mild neutrophilic leukocytosis developing after a severe hemorrhage.

3. In purpura, there is never any more anemia than can be directly attributed to blood loss.

4. In purpura, there is never any significant splenomegaly.

The diagnosis can be established by *sternal marrow biopsy* with sections as well as smears of the marrow. X-rays of the long bones may or may not be of value.

Comment.—The important questions arising from study of these cases have been presented in detail by Hickling. The controversy as to whether or not the myeloid metaplasia that exists is a form of leukemia or an intermediate "non-leukemic myelosis" or merely a compensatory mechanism will not be reopened here. It is sufficient to state that our current impression is that the various clinical, hematologic and pathologic findings in this group can be most readily explained as responses to invaded bone marrow; that the primary disturbance is replacement of marrow by foreign tissue; that the other changes are secondary and in the nature of compensatory attempts.

Summary and Conclusions.—A review of our thirteen cases together with those previously reported in the literature warrant the following conclusions:

1. Replacement of the bone marrow by foreign tissues (new bone, connective tissue, metastatic tumor, etc.) results in a clinical and hematologic pattern that is uniform and recognizable.

2. The characteristics that permit antemortem diagnosis are:

A. A progressive anemia, with moderate to marked anisocytosis and evidence of red cell regeneration consisting of a moderate increase in reticulocytes and a disproportionately large number of normoblasts.

B. A variable total white count, usually a moderate leukocytosis with a striking left shift in the granulocytes, the differential counts showing a few myelocytes and rare myeloblasts in all cases.

C. A severe degree of thrombocytopenia with clinical purpura.

D. Progressive splenomegaly.

E. Readily diagnostic abnormalities in sections of the sternal marrow, consisting of replacement of the normal tissue by tumor, connective tissue, or bone. It is important to emphasize the fact that these specific changes are seen only in marrow sections and will not appear in the usual puncture preparations.

F. Skeletal x-rays may reveal suggestive changes in the bones. These, where present, consist of slight variations in bone density.

3. The main differential diagnostic points between the bone marrow replacement picture and the two disturbances with which it is most often confused (myeloid leukemia and thrombocytopenic purpura) have been outlined.

4. Therapy consists of trying to aid the remaining functioning marrow elements with liver extract, iron and transfusions.

5. Splenectomy and radiotherapy to the spleen are contraindicated as the splenomegaly is due to the presence of areas of active compensatory blood formation.

BIBLIOGRAPHY

1. Hickling, R. A.: Quart. Jour. Med., 6: 253, 1937.
2. Dr. A. M. Pappenheimer's Final Note on Autopsy Protocol.
3. Jarcho, S.: Arch. Path., 22: 674, 1936.
4. Chapman, E. M.: Am. Jour. Med. Sci., 185: 9, 1933.

CLINIC OF DR. I. W. HELD

Beth Israel Hospital

CYSTS OF THE PANCREAS

Although the treatment of pancreatic cysts is surgical in the vast majority of cases, they not infrequently constitute a problem for the internist from the standpoints of diagnosis and preoperative and postoperative treatment. For this reason we believe that a discussion of this subject will be of interest to the general practitioner.

Pancreatic cysts are rare, it is true, but so is disease of the pancreas in general, with the exception of acute pancreatitis and edema of the head of the pancreas in the course of biliary duct disease. This rarity is due to the anatomic position of the pancreas. So great a protective factor is this that even in extensive abdominal injury the pancreas is seldom involved. It is also unusual for the pancreas to be involved when there is a suppurative process affecting almost every organ of the body. If a pancreatic abscess occurs, it is the result of a suppurative process in a neighboring organ or a sequela of acute pancreatitis and is rarely if ever an occurrence in the course of general sepsis. We have seen two cases of this kind. One patient had a gastric ulcer which perforated into the pancreas and was followed by a pancreatic abscess. After splenectomy and drainage of the abscess, the patient recovered completely. The other patient had an acute pancreatitis with chills, fever, pain in the epigastric region, and moderate secondary anemia. Functional tests revealed a diminution of pancreatic ferments in the stool and established a diagnosis of pancreatic abscess, verified at operation, to which, unfortunately, the patient succumbed.

Classification.—With regard to cysts of the pancreas, Körte has suggested the following very useful classification:

Retention cyst:
1. A cyst causing obstruction of the excretory duct of the pancreas (ranula pancreatica, Virchow)
2. A cyst resulting from interstitial pancreatitis with constriction of the medullary acini and small ducts

Proliferative cyst (cystadenoma)

Degenerative cyst:
1. Resulting from broken down tumors or autodigestion of encapsulated extravasations of blood
2. Resulting from degeneration of glandular lobules secondary to acute pancreatitis

Pseudocyst

Echinococcus cyst

Incidence.—In general, pancreatic cysts occur more often in the *female* than in the male. The *age* incidence varies from twenty to fifty, but cysts have occurred in children and in the aged. We have had one patient with a pancreatic cyst, a woman, who was seventy-eight years old. A congenital cyst of the pancreas secondary to fibrosis of the acinous portion and in the islands of Langerhans is occasionally encountered in children up to three or four years of age. The symptoms are abdominal pain, emaciation and anemia. A case of this kind with autopsy findings was recently shown at Mt. Sinai Hospital. The patient had succumbed not to the pancreatic condition but to pneumonia and, in discussing the case, Dr. Bela Schick pointed out that the respiratory infection might have resulted from a vitamin A disturbance brought on by the pancreatic disease. He called attention to the possibility, as pointed out earlier by Anderson, that many of these cases in the young, with emaciation, abdominal pain, fatty stool, and frequent upper respiratory infection leading eventually to death and interpreted as celiac disease, are actually cases of disease of the pancreas.

Cysts occur most frequently in the tail, less often in the body, and least often in the head of the pancreas, and they may so closely resemble a tumor of another abdominal organ or carcinoma of the pancreas that differential diagnosis is exceedingly difficult.

We recently encountered two cases of pancreatic cysts in women fifty-five and sixty years of age, respectively. The first symptoms were pain in the upper abdomen, nausea, and frequent vomiting which continued for several weeks. When the younger patient was admitted to Beth Israel Hospital, objective examination revealed an elongated, banana-shaped tumor in the upper right quadrant. It seemed to be multilocular and was rather freely movable. It was difficult to differentiate whether it belonged to the liver or to the head of the pancreas. The fact that there was no jaundice awakened the suspicion that it belonged to the liver. However, roentgenogram disclosed a characteristic pressure on the descending portion of the duodenum, indicating a diagnosis of cyst of the pancreas. Dr. I. Kross operated and the diagnosis of cyst was confirmed. Pathologic study later revealed that the cyst had degenerated into a carcinoma.

The second patient was seen through the courtesy of Dr. Arthur M. Weiss. She had exactly the same clinical and roentgenologic findings as the first one. The tumor likewise seemed cystic in nature, but proved to be a carcinoma of the body of the pancreas, approaching the head.

Retention Cyst.—Retention cysts occur most often in the tail of the pancreas. Most of them are unilocular but the cyst may be multilocular. The size varies from that of a strawberry to a grapefruit. Occasionally, a cyst grows to be as large as a child's head. The average cyst contains approximately 100 cc. of fluid, consisting chiefly of pancreatic secretions in which ferments, particularly diastase and lipase, can be demonstrated. Trypsin is sometimes demonstrable if the fluid is activated with enterokinase. The cystic contents may also include urea, cholesterol, calcium salts (particularly calcium carbonate) and occasionally a stone. When a stone is present it is difficult to decide whether the cyst is the result of the stone or the stone is the result of an accumulation of calcium in the cyst. The cyst may also contain remnants of pancreatic tissue, acini and lobuli.

The wall of the cyst, which may attain a thickness of 0.3 cm., is hard and fibrous and the inner surface is smooth unless there are inflammatory deposits, in which event it is irregular. Instead of an epithelial lining there are areas of connective

tissue containing numerous capillaries. If there is a co-existing chronic indurative pancreatitis, the amount of connective tissue is excessive.

Associated with the cyst one finds cellular degenerative or regenerative changes in the pancreas, due either to cystic pressure or to the deleterious action of pancreatic secretions. Changes are also evident in the pancreatic ducts, and new pancreatic ducts may actually develop. If there are stones in the pancreas, there is an associated inflammation and narrowing of the duct of Wirsung and its accessory ducts. When the cause of the cyst is an arteriosclerotic process there are changes in the pancreatic vessels. As a rule the islands of Langerhans are not affected—which explains the rare occurrence of diabetes in patients with a pancreatic cyst even when the cyst is located in the tail of the pancreas.

If the site of the obstruction that causes the retention cyst is immediately proximal to the duct of Wirsung there is a rosary-like dilatation of the entire duct; if the obstruction lies within the lumen of the duct, there is stagnation of pancreatic secretions and marked dilatation; and if the obstruction lies in one of the accessory ducts, there is dilatation of the terminal ducts and of the acini with the formation of little blebs (ranula pancreatica).

Proliferative Cyst.—Like the retention cyst, the proliferative cyst is usually located in the tail of the pancreas. It originates usually in newly formed glandular tissue (cystadenoma). Due to the fact that the glandular cells have a specific secretory function there is always an accumulation of secretion in the cyst. In some areas of the cyst there is an epithelial lining; in others this is absent due to digestion by pancreatic secretions. Deposits of pancreatic tissue and pigment are abundant on the inner wall of the cyst, with a proliferation of connective tissue containing alveoli with cylindrical epithelium. In some cases the connective tissue is so excessive as to cause the formation of a papilliform structure resembling a malignant tumor. Differentiation is made by the fact that the islands of Langerhans are not affected by the cyst.

The growth of a proliferative cyst is slow but continuous.

Degenerative Cyst.—The degenerative cyst is most often

encountered in syphilitics or alcoholics owing to the predisposition of their vessels to hemorrhage. Rich and Duff have shown that, as a result of increased intra-acinal pressure, pancreatic juice may escape and erode the capillaries or venules in the vicinity of the acini and even the arterioles supplying the acini, to the extent of bringing about necrosis of the vessels and an escape of blood, leading to hemorrhagic pancreatitis. Although it has been assumed that trypsinogen in the pancreas has to be activated by enterokinase into trypsin in order to be a digestant (Pavlow), Rich and Duff have demonstrated that escaped pancreatic juice can erode and digest the vessels without previous activation. It is the action of the tryptic ferment that is responsible for erosion of the pancreatic tissue and for hemorrhage, and the action of lipase that brings about fat necrosis.

Pseudocyst.—According to Körte,[1] pseudocysts occur more often than true pancreatic cysts. The pseudocyst begins as an inflammatory process in the neighborhood of the pancreas and spreads to the pancreas in the omental bursa. The initial cause is usually an injury to the pancreas, but in order for the injury to lead to the formation of a pseudocyst there must be hemorrhage into the omentum, penetration of the posterior wall of the omental bursa and closure of the foramen of Winslow. When blood and pancreatic secretions have collected between the pancreas and the peritoneum, a retroperitoneal peripancreatic cyst results. The cyst is not lined with epithelium and, as a rule, contains from 10 to 20 liters of fluid. If the pancreatic secretion continues to flow, the erosion of the blood vessels increases until an encapsulated hematoma develops.

A pseudocyst occurs very soon after trauma in contradistinction to the true cyst which forms, usually, long after injury.

Echinococcus Cyst.—An echinococcus cyst may be multilocular or unilocular, and may develop in any part of the pancreas. It is most frequent, however, in the head of the pancreas. This is probably due to the fact that invasion by the echinococci takes place through the large pancreatic duct. The outer surface of the cyst is smooth. The inner surface is lined with epithelium. The wall frequently contains many calcified deposits and within the cyst there are multiple echinococci.

SYMPTOMATOLOGY

Although the history and subjective symptoms are not as diagnostic as are the palpatory and roentgenologic findings, they must nevertheless be given careful consideration. Particularly diagnostic is a history of either recent or remote *traumatic injury* to the abdomen followed, immediately or within a few hours, by excruciating abdominal pain, with or without collapse, nausea and vomiting. If the pain radiated chiefly to the left side of the chest and to the left shoulder and was accompanied by obstinate constipation or symptoms of ileus, one can deduce with almost absolute certainty that there was an injury to the pancreas followed by acute pancreatitis or localized hemorrhage and eventually a cyst of the pancreas.

These symptoms may also be present in *rupture of the spleen* followed by a splenic cyst, but there are certain features that *differentiate* the two: In injury to the spleen, the shock is severe and the entire abdomen is markedly distended. The pain in the left hypochondrium is so intense that the patient will not tolerate even the lightest touch upon that area, due to stretching of the capsule of the spleen or rupture followed by perisplenitis. Even shaking of the bed causes unbearable pain. The pain in the left side of the chest is also so severe that the patient breathes with difficulty. The left dome of the diaphragm is pushed upward and the respiratory motion on the left side is so greatly restricted that there is a marked diminution in the breath sounds. If the elevation of the left dome causes atelectasis in the left base of the lungs, râles and diminished resonance or even slight dulness can be noted over the base of the lung. Another differentiating feature between splenic cyst and pancreatic cyst is that the pain in the former condition is much more likely to be spontaneous than is the pain of pancreatic cyst. This is also true of a *lymphatic cyst* when differentiating between a lymphatic cyst and a pancreatic cyst. The pain caused by pancreatic cyst is generally the result of pressure by the cyst on neighboring organs, interfering with gastric or intestinal motility. Recovery from the acute pain of a pancreatic cyst is followed by a feeling of discomfort and distress in the upper abdomen.

If the pancreatic cyst does not develop until long after in-

jury, there may be symptoms during the interval of a vague nature. These consist of periodic attacks of pain with resistance in the upper abdomen, a feeling of pressure in the epigastrium, and loss of weight.

If the cyst develops in the *body* of the pancreas and is large enough to press the stomach forward or backward, the patient will have more or less constant pain in the upper abdomen, radiating to the back. Vomiting and regurgitation are frequently present, and there may be extreme emaciation.

If the cyst is located in the *tail* of the pancreas, it may cause reflex cardiospasm, accompanied by regurgitation and vomiting. Hyperglycemia and glycosuria, however, are extremely rare. In only two of forty-one cases of this kind observed at the Mayo Clinic was there hyperglycemia. This low incidence is remarkable in view of the fact that hyperglycemia and glycosuria are transiently present in acute pancreatitis. It would seem that a cyst of the pancreas spares the islands of Langerbans.

When a cyst occurs in the *head* of the pancreas, it often causes pressure on the papilla Vateri and gives rise to persistent jaundice, even though the cyst be small. The jaundice is much deeper and more protracted than that caused by hydrops of the gallbladder.

A pathologic alteration, such as arteriosclerosis in the blood vessels of the pancreas, may be a predisposing factor in pancreatic cyst. If an individual already has a chronic pancreatitis, even the slightest trauma may lead to the formation of a cyst. In taking the history it is important to ascertain the *hour at which the injury was sustained.* If soon after a heavy meal, when the volume of the pancreas is at its maximum, the pancreas may be injured when otherwise it would escape.

Finally, with regard to the history and symptomatology, it must not be forgotten that pancreatitis can occur without known underlying cause and give rise to chronic localized degenerative changes with cyst formation. Cases have been reported following typhoid fever and in conjunction with stones in the gallbladder or pancreas.

OBJECTIVE FINDINGS

In order to evaluate more easily the palpatory findings, we offer, through the courtesy of Schmieden and Sebening,[2] a chart showing the various locations in which a pancreatic cyst may occur (Fig. 109).

Palpation usually reveals a solitary cyst of tense consistency. If the cyst is mobile, the degree of mobility is very slight. It is round or oval and is generally palpated more to the right than to the left of the umbilicus.
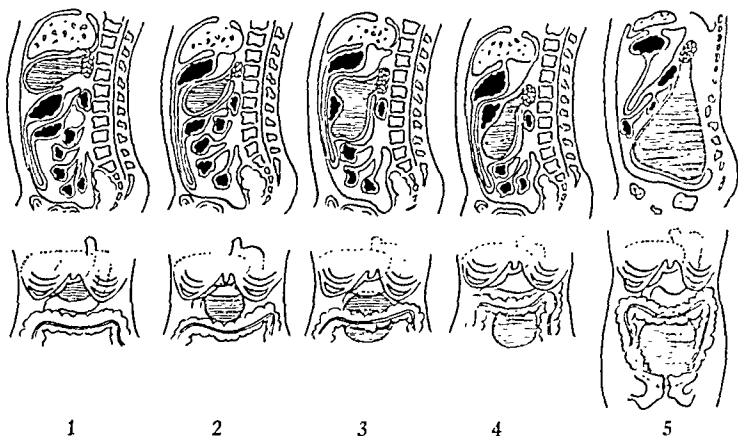
Fig. 109.—Sagittal and frontal aspects of cysts of the pancreas. 1, Cyst between liver and stomach. 2, Cyst between stomach and transverse colon. 3 and 4, Cyst between the transverse mesocolon. In 3 the colon lies at upper border. 5, Retroperitoneal cyst of tail of the pancreas with displacement of intestinal organs to the front and down to the small pelvis.

The percussion note over the cyst is flat or dull in contradistinction to the tympanitic percussion note over adjacent air-containing organs. An exception is the percussion note of a cyst located somewhat retroperitoneally, with displacement of the stomach and colon; in this situation the percussion note is resonant, almost tympanitic.

If the cyst is confined to the *head* of the pancreas, it is palpable almost exclusively in the right hypochondrium, somewhat above the umbilicus, and the pressure it exerts is largely upon the duodenum and biliary ducts. Such a cyst may simu-

late a large hydrops of the gallbladder or carcinoma of the head of the pancreas. Differentiation from hydrops of the gallbladder is aided by the fact that such a gallbladder is usually soft and mobile in contradistinction to the tense immobile nature of a cyst. Carcinoma may be differentiated by the presence of an associated enlargement of the gallbladder and jaundice (Courvoisier law) or metastatic enlargement of the liver.

If the cyst is in the *body* of the pancreas, it is usually palpable below the ensiform down to the umbilicus. If it fills the upper abdomen down to the umbilicus, it may be mistaken for a mesenteric cyst. Diagnosis may not be clarified until the patient undergoes exploratory operation. Such a large cyst must also be differentiated from *ascites, tuberculous peritonitis,* a cyst of the *lesser omentum* and a cyst of the *liver.* Differentiation between a pancreatic cyst and the latter two conditions is almost impossible without an exploratory operation. Differentiation between a pancreatic and omental cyst is particularly difficult if the cyst grows from a narrow pedicle into the gastrocolic ligament and lies below the stomach and colon. Some authors state, however, that a pancreatic cyst is more fixed than is an omental cyst.

When a pancreatic cyst lies very low in the pelvis and is slow-growing, differentiation must be made from an *ovarian cyst.* This differentiation is aided by the fact that, as a rule, a pancreatic cyst pushes the intestines characteristically to one side. Diagnosis will also be aided by a careful vaginal examination.

In the majority of cases the cyst is in the *tail* of the pancreas and is palpable to the left, and, sometimes also to the right, of the umbilicus. In rare instances it occupies the entire abdomen. When very large it may be mistaken for a cyst of the spleen. Differential features between the two have already been outlined.

It is important to remember, as emphasized by Albu and others, that pancreatic cysts may alter in size from time to time due to the fact that the cyst may empty itself spontaneously into the pancreatic duct and then refill.

Roentgen Findings.—Diagnosis is aided by filling the stomach and intestines with a contrast substance and noting any alteration in their contour or position due to pressure on

these organs by the cyst (Fig. 110). The tumor may so press on the lesser curvature of the stomach as to narrow its entire outline. A cyst in the tail of the pancreas may push the cardiac end of the stomach to the left or upward, or it may compress the pylorus and push both it and the duodenum downward. Feldman[3] has pointed out that a carcinoma of the head of the pancreas by compressing the descending portion of the duodenum disturbs the configuration of Kirkring's folds and manifests itself as an inverted 3 on the inner border of the descending duodenum. One would expect this finding also to be present when a cyst of the head of the pancreas causes similar
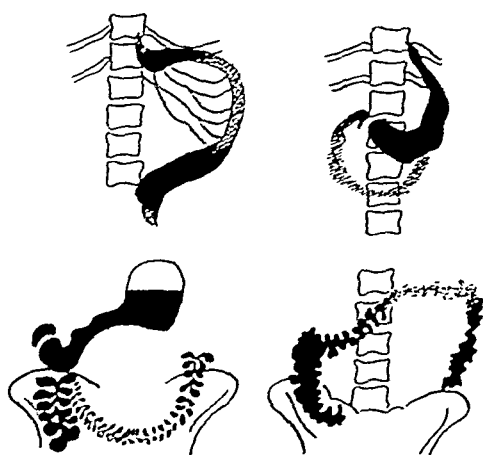
Fig. 110.—Displacement and change of form of the neighboring organs by pancreatic cyst.

pressure. The mucosal markings are displaced but not effaced by this pressure.

Some authors have advocated, as an aid to roentgen diagnosis, inflating the stomach either by giving the patient a Seidlitz powder or by introducing air into the stomach through a tube. But when the stomach is inflated by a Seidlitz powder, most of the air rises to the cardiac end and is quickly expelled by eructation. When inflated by means of injecting air through a stomach tube, the procedure is more troublesome to the patient than is warranted by the meager additional diagnostic information to be obtained in this way.

Occasionally one encounters a retroperitoneal cyst that is inaccessible to palpation. Roentgen examination may reveal that upward pressure of the cyst causes a marked indentation of the greater curvature of the stomach, with so much narrowing of the pars media that the stomach assumes a sandal shape, resembling the appearance of the stomach during infancy.

Other Objective Findings.—When *trauma* is suspected to have affected the pancreas, one should examine the urine and serum of the blood for diastase. Diminished diastase is an important diagnostic clue. The stool and urine should also be examined for trypsin or steapsin, but normal values will not exclude disease. During the acute stage, the trypsin content may be entirely normal and the diastase markedly reduced or absent. Another test of pancreatic function that may prove of aid is a secretin test recently described by Lagerlof.[3]

PROGNOSIS

If pancreatic cysts are not treated—and treatment is essentially surgical—the outcome will be fatal. Pancreatic cachexia usually precedes the death of the patient. Occasionally, death is due to the disease that originally caused the cyst, namely, chronic pancreatitis. In other cases, pressure of the cyst on the uninvolved pancreatic tissue causes acute necrotizing hemorrhagic pancreatitis. Death may also occur suddenly due to breaking through of the cyst into the abdominal cavity or into the intestines, followed by sepsis. Cases have been reported of the cyst breaking into one of the ureters and giving rise to fatal hemorrhage into the urinary bladder. Another cause of fatal termination may be erosion of the blood vessels with severe hemorrhage into the cyst, without perforation of the cyst into another organ. In still other cases, pressure of the cyst on the peritoneum causes the formation of localized peritoneal adhesions, accompanied by periodic attacks of pain and vomiting, and even fatal paralytic ileus.

TREATMENT

At one time surgical treatment was confined largely to puncture of the pancreatic cyst through the abdominal wall. Today this is known to be extremely dangerous and is seldom resorted

to even for diagnostic purposes. The preferred method of treatment is *incision* and *extirpation* of the cyst or, if the cyst is very large, it may first be *aspirated* and then be *injected* with an irritating substance that causes it to shrink.

When the diagnosis lies between a pancreatic cyst and carcinoma of the pancreas, surgical intervention is of the utmost importance because, if the lesion is a cyst, adequate surgical treatment will very often effect a cure.

In all cases, the closest cooperation between the internist and the surgeon is essential. As a rule, cysts develop slowly and medical treatment prior to surgical intervention is very important. The patient's *diet* should be regulated so that he will receive an adequate amount of highly nutritious food, quality rather than quantity being important. The meals should be small and frequent and should consist mainly of carbohydrates, easily digestible proteins, and a liberal amount of fruit juices. *Vitamins*, particularly B and C, must be included in the diet or taken in the form of commercial preparations (as, for instance, B-scorbic) in order to improve the patient's appetite and thus encourage a gain of weight. In the very rare cases in which hyperglycemia and glycosuria are present, the *carbohydrate intake* should be restricted and small doses of *insulin* administered once or twice daily. If the patient has *diarrhea*, he should be given 2.0 gm. calcium carbonate or calcium gluconate three times daily. If there is marked steatorrhea, all fatty food should be temporarily excluded. *Dehydration* should be prevented by the administration, for several days preceding operation, of 250 cc. of physiologic saline solution to which 50 cc. of 10 per cent gluconate has been added.

Postoperatively, the patient should be given physiologic saline and glucose intravenously, and perhaps also hypodermoclyses of Ringer's solution (500 cc.) daily for four or five days. If the patient is very anemic and emaciated, *small blood transfusions* should be given. If there is a tendency to diarrhea, calcium in the form of calcium gluconate (1 teaspoonful three times daily) should be prescribed. Steatorrhea and creatorrhea may be present postoperatively to an even greater extent than before operation. If this is so, the patient should be given small frequent meals consisting chiefly of fruit juices and car-

bohydrates, with a minimum of the most easily digestible fats (such as the fat contained in milk and sweet cream) until these symptoms have completely disappeared. After several weeks, butter may be allowed.

If, as occasionally happens, a *pancreatic fistula* develops following operation, the carbohydrate intake must be restricted and the Wohlgemuth ketogenic diet substituted. It is advisable, also, to prescribe a pancreatic substance such as pancreatin 1.0–1.5 gm. by mouth three times daily. This is best administered in conjunction with a mild alkali, such as 1.0 gm. of sodium citronate three times daily, after meals.

Finally, the patient's physical and mental activity must be restricted to a minimum for two or three months to allow him to recover completely from his exhausting operation.

BIBLIOGRAPHY

1. Körte: Die chirurgischen Krankheiten und die Verletzungen des Pankreas. Stuttgart: Enke, 1898. Dtsch. Chirurg. Lief. 45d.

2. Schmieden, V., and Sebening, W.: Arch. f. Klin. Chir., 148: 319–387, 1927.

3. Feldman, M.: Am. J. Dig. Dis., 6: 237–38, June, 1939.

4. Lagerlof, H.: Quart. J. Med., April, 1939, p. 115.

CLINIC OF DRS. LINN J. BOYD AND DAVID SCHERF

FROM THE DEPARTMENT OF MEDICINE, THE NEW YORK MEDICAL COLLEGE, FLOWER AND FIFTH AVENUE HOSPITALS

THE EFFECT OF SEDATIVES ON DIURESIS

CARDIAC patients who are decompensated and edematous frequently suffer from intractable insomnia which is often provoked by respiratory disturbances. Under these circumstances the somnifacient drugs often find consideration in the therapeutic program. Presumably morphine and its derivatives occupy first place among the measures which are utilized to relieve the dyspnea of cardiac patients. Accordingly, the physician is often confronted with a situation in which he must treat the edematous cardiac patient simultaneously with diuretic and sedative drugs. Analgesic preparations may also be indicated for the relief of pain.

Under these circumstances the narcotics, hypnotics and analgesics may exhibit a very pronounced influence on diuresis: They may *depress* it, and in this manner thwart therapeutic endeavors aimed to set diuresis into motion. Under certain conditions, however, they may *initiate* or *promote* diuresis, and accordingly exert an extremely useful and desirable effect. An awareness of the influence upon diuresis by agents which act upon the nervous system therefore possesses considerable practical significance.

One aspect of this problem may be illustrated by a few excerpts from some recent case histories:

Case I.—M. G., a fifty-two-year-old Puerto Rican female, entered the Hospital because of shortness of breath and palpitation. Effort dyspnea and ankle edema had been present for two years. On the day before admission dyspnea became extreme and palpitation marked. Examination disclosed an enlarged heart with a systolic murmur at the aortic area and an accentuated

second aortic sound. The blood pressure was 160/90. There were fine crackling râles at both bases and the liver edge was palpable three fingers below the costal margin; there was marked edema of the extremities. The cause of her congestive failure was cardiac dilatation secondary to coronary sclerosis.

On the sixth day of hospitalization the patient was given 2 cc. of mercupurin intravenously. The fluid intake during the next twenty-four hours was 1,000 cc. and the output 1,300 cc. For experimental purposes, she was given the same dose of the diuretic on the eleventh day of hospitalization. On the day preceding the injection and the day of the injection, she received 1.5 gm. of aminopyrine. *The fluid intake was 1,000 cc. and the output 600 cc. during the twenty-four-hour period following the injection.* Accordingly, the output was less than one-half the excretion when no aminopyrine was used, despite the fact that the edema and related symptoms were as severe as at the time of the first injection.

Case II.—M. W., fifty-two years old, entered the hospital because of extreme shortness of breath. She had suffered from dyspnea on slight effort, palpitation and swelling of the ankles for ten years. There had been attacks of palpitation, nocturnal dyspnea, and precordial pain. In addition to marked dyspnea, orthopnea and cyanosis, examination revealed a markedly enlarged heart with systolic and diastolic murmurs at the mitral area and a systolic murmur together with an accentuated second sound at the aortic area. The blood pressure was 190/110. There were crackling râles in both lung fields, the liver edge was palpated four fingers below the costal margin, and there was marked edema of the legs.

With a fluid intake of 1,000 to 1,200 cc. per day, the output amounted to approximately 600 cc. per day. Following the injection of 2 cc. of mercupurin intravenously, the output rose to 1,750 cc. during the next twenty-four hours. After two days of aminopyrine, 1.5 gm. each day, mercupurin was injected in the same dose as before and the ouput was 300 cc. on that day; on the following day, the aminopyrine was continued and the output fell to less than 200 cc. When aminopyrine was discontinued the output rose to its original level.

The above examples are unselected except in the sense that the writers avoid this type of sedation as far as possible prior to or coincident with diuretic therapy and these experiments were conducted simply to exemplify an important point.

It would be expected from the start that diuresis would be influenced by narcotics. There is an extremely rich nerve supply to the kidneys; the action of drugs affecting the autonomic nervous systems upon diuresis has been established. There is clinical and experimental evidence which indicates that diuresis is influenced by the central nervous system. Moreover, drugs acting upon the nervous system can also affect the blood supply of the kidney and modify its secretory func-

tion by an alteration of vasomotor tonus; they can also influence the production of hormonal substances which promote and depress diuresis. Finally, drugs can also influence the processes of fluid exchange between tissue and blood, in the tissues, and can act particularly upon the renal tissue itself.

The very multiplicity of these possible modes of action makes it comprehensible why an exact analysis of them soon encounters difficulties. Two factors may act in the same direction, complement or antagonize each other, so that very complex situations, difficult to unravel, are presented. Although medicine is only imperfectly informed about the diuretic and antidiuretic action of somnifacients, clinical and experimental investigations are available concerning the extent and frequency of this effect and provide, to some extent, quite uniform results:

Effect of Hypnotics on Diuresis.—The first animal experiments on the effect of hypnotics upon diuresis extend quite far into the past. In 1888, v. Schroeder found that the diuretic effect of *caffeine* was partly abolished by the stimulating action of this drug upon the vasomotor nerves and the diminution of the blood supply of the kidney resulting from this. For this reason the author attempted to abolish the vasoconstriction produced by caffeine in rabbits by combining caffeine with chloral or paraldehyde; he found that diuresis was actually augmented by this. Earlier, Langgaard had studied caffeine diuresis in chloralized rabbits and subsequently Huchard warned against using morphine since it "paralyzes the kidneys."

A series of investigations concerning the influence of hypnotics on diuresis were published by E. P. Pick and his pupils. They emerged from studies on pituitrin antidiuresis and its influence by narcotics. These studies not only prove that diuresis is altered by *hypnotics* and *sedatives*, but also indicate that the individual narcotics *do not act uniformly*. Narcotics can be divided into two large groups in respect to their action on diuresis. The so-called mesencephalic group (*phenobarbital, chloretone*) *depress* diuresis, an action ascribed to depression of the diuresis centers. Drugs acting upon the cortex (*chloral, paraldehyde*) *augment* spontaneous diuresis as well as the diuresis provoked by caffeine and theobromine, since

they abolish the normal depressant action of the cerebral centers. Water and salt diuresis are not affected in a parallel manner but in entirely different ways.

Subsequently, many contradictory results were obtained. Contradictions chiefly arose owing to the fact that animal experiments were not always performed under identical conditions:

For example, various species as well as various races of animals were employed, and this is not without significance in rabbit experiments. The nutriment of the animal was not always the same; the administration of fluid in an experiment at times was accomplished through an esophageal or duodenal sound, but at other times intravenously; likewise, the amount of liquid varied and the experiments extended over various lengths of time and the intervals elapsing between the individual experiments on the same animal were not always identical. Finally, different doses of the narcotic led to entirely different results.

In this manner, to mention but one example, Epstein found that luminal, which otherwise *depresses* diuresis, *increases* diuresis when the *intravenous* introduction of water is employed in an experiment. He explains this as an abnormal central regulatory event which is produced by the sudden hydremia; thus the centers react differently to various narcotics.

If the least alteration of the experimental arrangement suffices to modify the results even in the animal kingdom, naturally this situation prevails to a vastly greater extent in the human, and especially in the sick, individual. In patients, both the tissues and centers may react in an entirely different manner than in the healthy individual, so that *"paradoxical"* reactions appear just as they are encountered in animal experiments when the animal has received preliminary treatment with certain poisons. Not rarely the extent and manner of response varies from day to day since the individual factors regulating diuresis undergo frequent alterations in cardiac patients. Thus it happens that even brief experiments in man cannot be compared with one another. Despite these difficulties a large amount of data has also been assembled in the clinic.

Effect of Morphine on Diuresis.—Many years ago morphine and its derivatives were recommended as important agents for supporting digitalis therapy in patients with cardiac decompensation. Obligatory indications for morphine are *cardiac asthma* and *pulmonary edema*. After the administration of moderate amounts of morphine one may observe not only an amelioration of the dyspnea, but also a decrease of

hepatic enlargement and an increase of diuresis. These therapeutic actions may be explained as indirect effects on the circulation through the reduction of dyspnea and the subsequent improvement of the heart. In older literature morphine was designated as a cardiac tonic: "Morphine is a second digitalis!" Accordingly cases of myocardial disease may be observed in which massive diuresis and decisive improvement appear without any other therapy save *one injection* of morphine.

On the basis of abundant clinical material it has been demonstrated that a definite increase of urinary output occurs after *morphine, pantopon,* and *chloral hydrate.* On the other hand, *phenobarbital* and *veronal* were without effect, according to Hopmann. This observer believes that the promotion of diuresis by means of morphine is the result of a decrease of motor unrest rather than a consequence of lessened dyspnea. According to the same investigator, the increase of diuresis after the administration of morphine often is not distinct in dyspneic individuals and, on the contrary, may be very apparent in patients without dyspnea. Hopmann also believes that an influence on renal blood supply (effect on vasomotor centers) by morphine can be eliminated. He stresses the observation that morphine particularly increases *nocturnal* but not *diurnal* diuresis, so that morphine effects recall, to some extent, nycturia.

According to Macrez, *chloral* is preferable to the *barbiturates* in decompensated cardiac patients.

On the other hand, if renal function is tested by the administration of 1500 cc. of water given within a period of thirty minutes while the patient is under the influence of morphine, an unequivocal depression of diuresis is found in normal individuals; the same results were obtained in renal diseases of various types. The addition of *atropine* or *epinephrine* to morphine did not abolish the depression. The results of these investigations, performed on healthy individuals, do not contradict those obtained in decompensated cardiac patients. The effect of morphine is complex and the indirect diuretic effect in cardiac patients has other points of attack than the inhibitory effect on the normal kidney. Morphine assumes an intermediate position between the cerebral and mesencephalic narcotics.

Effect of Analgesics on Diuresis.—The following observation possesses greater practical significance and is illustrated by the clinical excerpts presented earlier: not only outspoken narcotics, but also analgesic agents such as *antipyrine* and *aminopyrine,* which are more frequently employed, can influence diuresis:

On the occasion of his observations on the antipyretic effect of *aminopyrine,* Gessler noted that in addition to numerous other metabolic effects, this agent also depresses water and salt diuresis. Averbuck also found a depression of water excretion but not of salt diuresis after the administration of this drug to rabbits. At the same time Scherf studied the effect of aminopyrine on the diuresis of man. In a patient suffering from endocarditis it was striking that a marked decrease in the output of urine occurred simultaneously with the fall of temperature after the administration of 1.5 gm. of aminopyrine per day. When the drug was discontinued, the fever rose again and a copious outflow of urine followed. Systematic investigation of the effect of aminopyrine on fifty individuals (healthy, compensated, or decompensated cardiac patients and those with various other illnesses) revealed that 84 per cent of those studied showed a distinct increase of weight produced by water and salt retention after the administration of 1.5–2.0 gm. of aminopyrine daily for five days. In many instances the increase of weight amounted to more than 2 kg. Those with normal circulations also showed decreased diuresis, but the reduction of urinary output was more evident in patients with edema or those tending to manifest it. No explanation was offered for the fact that 16 per cent of the group failed to react to aminopyrine.

Not only *spontaneous* diuresis, but also the effect of the *purine* or *mercury* diuretics is completely abolished by aminopyrine in a majority of patients. Patients who lose 6 to 8 pounds within twenty-four hours as the result of marked diuresis following the injection of a mercurial diuretic, do not react at all if the same diuretic is administered in the same dose while they are under the influence of 1.5–2.0 gm. of aminopyrine daily; as a matter of fact the weight may be even increased on the following day. In the same manner aminopyrine diminishes the thirst and thereby the ingestion of water

in diabetes insipidus. Here also the excretion of chlorides is depressed in a parallel manner to the excretion of water. Augmentation of diuresis by aminopyrine was not encountered.

If a dog in which a bladder fistula has been produced is given a 5 per cent aminopyrine solution intramuscularly and, simultaneously, 200 cc. of water is introduced into the stomach by means of a tube, a complete depression of diuresis is observed (Fig. 111). This persists for several hours. If the same experiment is repeated and 8 gm. of urea are administered in addition, the urea being administered by mouth, then

————— I GRAM AMINOPYRINE + 200cc. H_2O
------ I GRAM AMINOPYRINE + 200cc H_2O + 8 GRAMS UREA
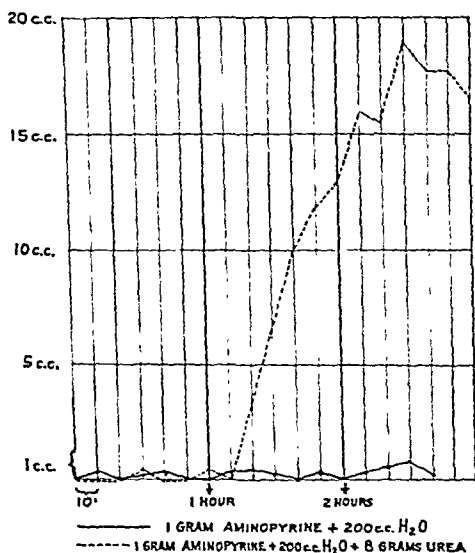
Fig. 111.—Complete depression of diuresis by aminopyrine.

the decrease in urinary output is interrupted after forty to sixty minutes. Hypertonic glucose solution administered intravenously acts similarly. Accordingly, "renal diuretics" unfold their action despite the simultaneous administration of aminopyrine.

The effect of hypnotics and sedatives on diuresis of patients with *diabetes insipidus* has been carefully studied. But it should be anticipated that the results of observations upon healthy individuals, compensated and decompensated patients cannot be compared with those observed in diabetes insipidus;

this peculiarly obvious fact often has not received adequate consideration. More recently Kahn confirmed the beneficial effect of aminopyrine in diabetes insipidus and recommended it in combination with pituitary preparations.

Comment and Summary.—In general the clinical and experimental investigations described above teach that agents which act upon the central nervous system influence diuresis even when they are administered in the usual therapeutic doses. This influence is exerted in the healthy individual, but it can also be demonstrated in patients suffering from renal diseases and in some individuals with cardiac disease and is expressed predominantly as a depression.

Accordingly, care should be observed in the employment of the compounds mentioned in treating patients with edema or those exhibiting a tendency to it. But while aminopyrine and related preparations *depress* spontaneous diuresis, in some circulatory patients an increase of urinary output is observed after the use of morphine and chloral hydrate and, under definite conditions also, after phenobarbital. To some extent, at least, this depends upon the action of the agent on the *inhibiting* cortical centers.

Exact details on the point of attack and concerning the working mechanism of these agents are unknown. If their employment should be necessary over a long period of time, then *serial determination* of the body weight is absolutely indicated in order to detect latent edema or to follow the course of manifest water retention.

CONTRIBUTION BY DRS. FRANZ M. GROEDEL AND BRUNO KISCH

New York

STROPHANTHIN THERAPY IN HEART FAILURE*

Although the value of strophanthin, a drug introduced for intravenous cardiac therapy by the late A. Fraenkel, is generally recognized in Europe, it is not fully appreciated by the American physician. In fact it is almost as unpopular in America as it is popular in Europe, and somewhere between the two extremes of enthusiasm and rejection must lie the truth. In order to help establish this we are offering this summation of our experience with strophanthin. We have found it indispensable in the treatment of many cases of heart failure.

What Is Strophanthin?—In the early part of the nineteenth century the first plants containing strophanthin were brought from Africa to France where the botanist, Descandolle, gave the plant, a genus of poisonous apocynaceous plants, the name "Strophanthus" because of the shape of the flower.

Next, a botanist member, John Kirk, of Livingstone's expedition to the Zambesi (1853–56), brought back an arrow poison that had proved particularly useful to natives in hunting elephants. This poison, or "kombe" as the natives called it, was accidentally discovered by Kirk to be a heart poison. This was proved to be the case in 1872 by Thomas R. Fraser, an English scientist, who found out that the arrow poison in question was identical with the poison prepared from the seeds of the Strophanthus. Several years later (1890) he was able to describe the method of obtaining strophanthin (a method still in use today), and to explain its chemical properties.

* In Memoriam to Prof. Dr. A. Fraenkel, who died at Heidelberg in December, 1938.

Prior to that, however, Hilton, Fagge and Stevenson[1] (in 1865) had shown that strophanthin was a "cardiac poison" with an active principle similar to that of digitalis glucosides. Administering it to the frog, they found that it stopped the frog's heart, which became contracted and pale.

Meanwhile, French scientists discovered that there are various species of Strophanthus and that they yield different active principles, even when chemically treated in an identical manner. For example, *S. glaber* gives a crystalline and *S. kombe* an amorphous product, both capable of affecting the heart. In 1888 Arnaud succeeded in producing a crystalline substance from the wood of a tree, *Acocanthera ouabaio,* in Somali, which was identical with the strophanthin produced from *S. gratus.* He called the product "Ouabain." There are now forty-three known varieties of strophanthin. The three most important are *S. gratus, S. hispidus,* and *S. kombe,* known commercially as *g-strophanthin, h-strophanthin,* and *k-strophanthin,* respectively.

Strophanthin, like the digitalis bodies, is a glucoside, which means an ether-like combination of sugar with another substance. In the process of chemical splitting up, the glucoside takes up water and becomes separated into sugar and a sugar-free component, the so-called "genin" or aglycon. The genin is very similar in all varieties of strophanthin and is likewise very similar to the genin of the digitalis glucosides. Only the sugar is different, with variations in solubility. The genin of both the strophanthin and digitalis glucosides is chemically very closely related to cholesterol and bile acids.

Even the slightest alteration in the molecules of strophanthin affects the drug's activity. Therefore, manufacturers must, for instance, exercise the utmost care in selecting the right type of glass for the ampules to maintain the degree of action of the strophanthin at a constant level.

Briefly summarizing the answer to the question "What is strophanthin?" we may then say that it is a glucoside obtained from Strophanthus seeds and is very closely related to digitalis glucosides.

The Action of Strophanthin.—Modern analysis of the circulatory effect of strophanthin has revealed that there is no essential difference in the action of strophanthin and the dig-

italis glucosides.   Their effects on the heart in failure are as
follows:

1. *Delay in the creation of sinus impulses.*   This is brought
about by an increased vagus tension.   The increased vagus
tension in turn is caused by an increased blood pressure in the
area of the pressoreceptoric nerves and is partially caused by
the decrease of pressure in the auricles and veins close to the
heart (Bainbridge-reflex).   Whether or not a central increase
of the tone of the vagus is caused directly by digitalis or stro-
phanthin is still a moot question, as is also the chemical influ-
ence of digitalis or strophanthin on the end apparatus of the
pressoreceptoric nerves.

2. *A change in the action of the heart muscle.*   Digitalis
causes an intensification of the systole and deepening of the
diastole.   This change in action is noticeable not only on the
ventricles, but also, though in much less degree, on the auricles
(W. Straub[2]).   This direct action of the digitalis glucosides
on the heart muscle is as indisputable as is the hemodynamic
factor.

3. *An increase of the minute volume of the heart.*   This is,
first of all, the consequence of increased strength in the decom-
pensated heart and probably is combined with changes of the
circulating blood volume.   Strophanthin enables the heart in
failure to master the higher afflux of venous blood.

4. *Large doses of the digitalis glucosides may produce, both
directly and indirectly* (due to sinus bradycardia), *heterotopic
heart impulses* (extra systoles, bigeminie, trigeminie, fibrilla-
tion) *and disturbances in conduction.*

5. *The digitalis glucosides and strophanthin also produce
certain changes in the electrocardiogram,* especially in the T-
wave and the ST segment, changes for which Kahlson[3] has
given an excellent explanation.

Strophanthin, in contradistinction to the digitalis glucosides,
was formerly thought to have a very weak effect on the vagus
and a very pronounced influence on the heart muscle.   This
difference is now known to have no basis in fact.   All of the
effects of digitalis glucosides mentioned above also follow the
administration of strophanthin.   Differences are the result of
dosage and technic of administration and are not essential
variations, with one exception: One result of the administration

of all the digitalis glucosides is an accumulation, due to chemical binding, of glucosides in the cells, particularly in the cells of the heart. This accumulation, as shown experimentally and noted in clinical experience, is less pronounced after the administration of strophanthin than after any of the digitalis glucosides.

Administration of Strophanthin.—Following Withering's establishment of the scientific foundation of digitalis therapy, nothing of equal importance was done until intravenous strophanthin therapy was introduced in 1906 by A. Fraenkel.[4] Shortly before this, Kottman[5] ventured to recommend the intravenous administration of digitalis, but digitalis preparations were not yet chemically pure. Fraenkel's immortal contribution was that he made possible an exact dosage of a chemically pure preparation of a digitalis body, the strophanthin in clinical treatment.

The oral administration of a few drops of tincture of strophanthus in cases of heart failure is only a symbolic gesture. This is readily apparent from the fact that the average optimum intravenous dosage of k-strophanthin is 1/200 to 1/150 of the oral dosage. Tincture of strophanthus (an alcoholic extract of the seeds) cannot, of course, be compared in strength to strophanthin (a glucoside of the strophanthus seeds). Absorption of strophanthin in the stomach is extremely meager.

The subcutaneous injection of strophanthin is inadvisable due to the local irritation that results therefrom. Moreover, this method is uncertain with regard to degree and time of absorption of the drug and has been discarded, generally, in favor of more satisfactory methods of administration.

The sublingual administration of strophanthin has been recommended by E. E. Cornwall[6] but has few adherents. The first experience with this method was that of Kirk, when he cleaned his teeth with a brush contaminated by Kombe arrow poison and suffered a heart reaction that was later discovered to be typical.

The classical method of strophanthin administration is by *intravenous injection*, introduced by Fraenkel. We call this method "classical" because it makes possible the introduction of an absolutely exact dosage of the drug into the blood stream with the quickest possible action. Intravenous strophanthin

therapy, however, is *not* applicable to every case of heart failure. If the skin and venous walls are damaged, for instance, due to too many intravenous injections, the intravenous injection of strophanthin is painful if not impossible for both patient and physician. Patients are encountered also who refuse every kind of intravenous treatment. The substitute method of intracardial injection, which has been recommended by some authors, is a little too heroic and is to be carried out only in emergency cases. The method of Castaigne[7] of injecting strophanthin intraperitoneally likewise has not found many followers. Intramuscular injection is painful though it has become somewhat more applicable due to improvement in the preparations now available.

The most satisfactory substitute for the intravenous method seems to be *rectal strophanthin therapy*. Pribram[8] complained in 1931 that the latter therapy was being neglected and that the believers in it were too few. This attitude began to change when one of us[9] pointed out the following advantages of the rectal injection of strophanthin dissolved in 10 cc. water: The chief advantage is that drugs introduced into the rectum undergo at most a very slight chemical alteration. Moreover, they reach the blood stream via the hemorrhoidal plexus and the hypogastric vein without entering the liver. It is true that the time and degree of absorption cannot be as exactly controlled by the physician as when strophanthin is given intravenously. Therefore one of us (Groedel[10]) has recommended the occasional addition of 0.5 gm. methylene blue to the injection. The interval between the injection and the appearance of dark urine is an indicator of absorption time.

Indications for Strophanthin Therapy.—Since strophanthin does not differ essentially in action from the digitalis glucosides, the indications for its use are identical with those for digitalis therapy. Many European clinicians use only strophanthin in cases of heart failure. Others still feel that it is more dangerous than digitalis. In the authors' experience, the indications and contraindications for strophanthin therapy are, in general, those for digitalis therapy. Strophanthin therapy does require, however, more careful observation and greater experience than does digitalis therapy. This is because the therapeutic dose of strophanthin is nearer to the toxic dose

than the therapeutic dose of digitalis. In this regard, the rectal method of administration has an advantage over the intravenous method inasmuch as it has been shown experimentally that 10 to 20 times as much can be given safely by rectal application as can be given safely intravenously.

Many patients who no longer respond to digitalis can be improved, often for a relatively long period of time, under the prolonged administration of strophanthin. This fact alone makes it obligatory upon every physician to be familiar with strophanthin therapy. Strophanthin is also particularly valuable in the treatment of patients with such a high degree of stasis that the absorbability of the stomach, intestines and even of the tissues is greatly diminished or absent. In our experience, when treating an emergency case, it is better to administer strophanthin intravenously than to digitalize with maximal doses of digitalis, as recommended anew recently by Eggleston.[11] Strophanthin also has an advantage over digitalis in the treatment of patients with heart failure characterized by slow heart action because it is less conducive to bradycardia than is digitalis.

If digitalis has already been given, strophanthin should not be administered before twenty-four to thirty-six hours have elapsed following the last dose of digitalis. Fraenkel, however, with an experience greater than that of any other clinician during his lifetime, was not averse to eliminating this interval altogether—provided the initial dose of strophanthin was very small (for instance, 1/400 grain).

If strophanthin therapy has to be discontinued and digigitalization begun, there need be no interval between the two.

In addition to its therapeutic value, strophanthin is of diagnostic use in differentiating between organic and functional heart insufficiency—insofar as improvement after the application of strophanthin proves that there was heart failure present.

Dosage of Strophanthin Alone, and in Combination with Other Remedies.—Most of the accidents that happened at the beginning of the strophanthin era were due to too high dosage. Since the adoption of a smaller dose—as a rule, less than 1/100 grain per diem—the results have been excellent. Fraenkel stated in 1928 that in nineteen years' experience with strophanthin he had not seen a single case of strophanthin

damage. Many other European clinicians, particularly Vacquez who uses the form of strophanthin known as "Ouabain," have had a similar favorable experience.

For the first *intravenous* injection 1/400 to a maximum of 1/300 grain should be given. Fraenkel preferred k-strophanthin for intravenous application because the gap between the therapeutic and toxic dosage is greater than it is in g-strophanthin or h-strophanthin.

When using the method of *rectal* administration, as much as 1/50 grain of strophanthin can be safely and effectively administered one to three times daily.

When injecting strophanthin intravenously, regulation of the *speed of injection* is of the utmost importance. The slower the injection, the more beneficial will it be. This speaks in favor, of course, of the rectal method—provided the rate of absorption is carefully checked by the occasional inclusion of 0.5 gm. methylene blue in the dosage of strophanthin. In every case the optional dosage for the individual patient's heart and circulation must be accurately ascertained at the beginning of treatment. This is true of digitalis as well as of strophanthin therapy. According to Fraenkel, hypertensive, febrile, and thyrotoxic patients require a higher dosage than do other patients.

The *effect* of strophanthin intravenously injected is usually noticed within a very few minutes, but it is not as enduring as is that of an equivalent digitalis administration. The benefit usually continues for several days, especially when compensation has once been restored. One two-hundredth of a grain daily can be given intravenously for a very long time (week or months) without risking its accumulation in the cells of the heart. Doses of 1/100 grain are rarely necessary and should be overstepped only under exceptional circumstances, for instance, when the smaller dose is not producing a satisfactory result. However, if the patient has become refractory to other digitalis bodies and treatment with strophanthin must be continued for a long time, a larger dose (1/100 grain) may be given twice a week.

Many other remedies for heart failure can be given simultaneously in the syringe with strophanthin. In fact, it is even advisable to include 10 cc. of glucose (10 to 15 per cent) for

the reason that the additional fluid lessens the difficulty of administering strophanthin slowly.

Remedies of the xanthine group—for example, *metaphyllin*, *euphyllin*, *aminophyllin*, et cetera—may be added to the strophanthin in small quantities as soon as the patient's reaction to strophanthin is known. *Diuretics, i.e.,* the modern mercury preparations, may be added as required. *Metrazol* and *coramine* are occasionally advisable as an additional remedy in an emergency. To avoid shock, more than 0.5 cc. of metrazol or coramine should *not* be given at any one time. If more is required it is better to repeat the injection several times daily. According to the literature it is not advisable to combine the intravenous application of strophanthin with calcium.

The *technic* of intravenous injection is too well known to need description here. With regard to the rectal administration of strophanthin, however, we would recommend a minimal initial dosage of 1/100 grain of strophanthin (to be increased soon to 1/50) regardless of the type of strophanthin. Either the ampule or the cheaper tablet form (diluted in a maximum of 10 cc. of lukewarm water) may be used. It is administered with a 10 cc. syringe to which a 3 or 4 inch piece of small ureter catheter has been attached. Rectal application is best carried out after defecation and, if possible, after cleansing the rectum by an enema of 200 cc. some time before the injection. It is inadvisable to add glucose to the rectal injection. Even 5 per cent glucose rectally applied is not absorbed by many patients. Aminophyllin, euphyllin, and, above all, mercury preparations, are irritable to the rectum and should *not* be given in that manner when the patient is under rectal strophanthin treatment.

Results of Strophanthin Therapy.—Since there is no better way to illustrate the value of an advocated treatment than case reports, we are presenting a few typical cases. Before doing so, however, we wish to call attention to the *signs* of having *overstepped the optimal dose*. These signs are (as after an overdose of other digitalis glucosides) increased vagus action, extrasystoles, prolongation of conduction time, and ventricular fibrillation. The simultaneous administration of small doses of euphyllin or a similarly acting drug to counteract narrowing of the coronary arteries will diminish the risk of extra-

systoles and ventricular fibrillation. All danger signs can be avoided by starting with a *minimal* dose of strophanthin, giving always comparatively small doses, and by constantly watching the patient's reactions very carefully. The electrocardiograph should be utilized not only at the beginning, but several times during treatment.

Case I.—The first patient we wish to present is one with severe myocardial damage who is now seventy-five years old. When he first came for consultation in 1927, he stated that he had had an attack of angina pectoris three weeks previously which kept him in bed for two weeks. When he was next seen in 1930 he stated that milder attacks had recurred often during the intervening years. He was now also complaining of breathlessness, coughing and insomnia. A serious motor accident in January, 1934, increased these symptoms to such an extent that he could no longer lie flat without marked air hunger, and this was present, though to a less degree, even in a sitting posture. The anginal attacks had increased in frequency and there was now noticeable swelling of the feet. Between 1927 and 1934, physical examination at various times revealed the following: Slightly distant cardiac sounds; first sound murmur-like, second sound at the base accentuated. Orthodiagrams showed the size of the heart to be 15.5 cm., average. ECG: T₁, normal R. The blood pressure average 135/80. The urine showed constant traces of albumin and a normal specific gravity. The Wassermann examination was negative and the blood findings were normal.

From 1927 to 1934 the patient received intermittent medication with theobromine and digitalis, an occasional series of iodine injections, and nitroglycerine during his attacks of stenocardia.

In July, 1934, it was noted by roentgen examination that the size of his heart had increased (to more than 18 cm. average), and that there was a slight exudate in the right side. Physical examination revealed slight hepatic enlargement, considerable edema and congestive catarrh. There was a slight systolic murmur. Electrocardiographic examination revealed an inversion of T I and widening of the R waves; the chest leads showed inversion of the T in lead CR 5 (left ECG), widening and notching of the R in lead CR 2 (right ECG). The findings indicated that, in addition to left ventricular hypertrophy due to generalized arteriosclerosis, there was now muscular injury localized in the right ventricle.

A week of hospitalization resulted in a satisfactory though imperfect compensation. During this time the patient received the following medication: salyrgan twice a week, a daily suppository of 0.12 gm. digitalis, 1 gm. of diuretin twice daily, and morphine-atropine at night.

Following hospitalization, the patient went to a spa where he took one digitalis suppository every second day and 0.5 gm. of diuretin twice daily. He was also given pantopon injections as a soporific. His condition improved very little and compensation remained imperfect.

On his return to the city, in September, the patient overexerted himself and experienced three attacks of weakness with stenocardia, the last of which

provoked nocturnal pulmonary edema. For the first time, definite gallop rhythm was noted. The pulse rate was above 90. The blood pressure was 110/90. The liver was enlarged. Immediate medication consisted of subcutaneous digifolin, morphine, cardiazol, camphor in oil, followed by digitalis suppositories and diuretin twice daily. The gallop persisted and the pulse rate remained above 90. Strophanthin, 1/200 and later 1/100 grain was now administered intravenously in 10 per cent glucose solution once daily.

There was immediate improvement of the subjective condition. After the fifth injection the gallop rhythm disappeared and the pulse rate dropped to 70. Later, injections were given only every second day. The pulse remained at 60. The hepatic swelling disappeared. After one month, with the patient free of pain, intravenous strophanthin therapy was discontinued.

During the next four weeks the patient was given one intramuscular injection of iodine and arsenic daily. He also took a digitalis suppository every second day and 0.5 gm. diuretin twice daily. The pulse rate remained below 80. There was no gallop rhythm. The hepatic swelling had not returned. His general health was good.

During the next three weeks the patient again overexerted himself. Consequently, his edema, hepatic swelling and cough recurred. The pulse rate rose to 80. A milk diet for a few days was only temporarily effective. At the end of this time, the patient was brought home from the "movies" one afternoon suffering from angina pectoris and pulmonary edema. Gallop rhythm recurred and his pulse rate was 90. The pulmonary edema was overcome by the usual methods. Camphor in oil was given repeatedly but no digitalis was allowed for thirty-six hours.

Intravenous strophanthin therapy was indicated, but could not be started because the patient was about to leave for the south and could delay his trip only ten days. Intravenous strophanthin treatment while in the south at the place where he was to be would be impossible. In view of this, we decided to test the effect of rectal strophanthin, hoping to find it better than the digitalis treatment and a more adequate method of permanent treatment. We started with 1/100 grain of strophanthin in 20 cc. of water, injected daily into the rectum with a 20 cc. syringe. In addition, 0.5 gm. diuretin twice daily, and pantopon at night was prescribed as a soporific. The condition improved immediately. Within four days the pulse rate dropped to 70 and the gallop rhythm disappeared. The frequency of the injections was then reduced to one every second day. The pulse went down to 60. The patient then left for the south with instructions to continue the following therapy permanently: 1/100 grain of strophanthin in 20 cc. water every second day by rectum; and 0.5 gm. diuretin twice daily by mouth; fewer injections when the pulse rate should drop below 60 and vice versa.

The patient bore the two-day trip south well and during the ensuing year his condition remained good under rectal strophanthin therapy. In the winter of 1935–36, his Florida physician prescribed digitalis by mouth and the patient's condition began to grow continuously worse. When he returned to New York in June, 1936, examination revealed that both the heart and liver were very much enlarged. The lungs were congested, and there was gallop rhythm. He also had a strong cough.

After a few days of rectal strophanthin therapy (twice daily 1/100 grain) the condition improved. The rectal strophanthin therapy was continued and the patient remained in a satisfactorily compensated condition until 1938, when he was seen by us for the last time. He died in 1939.

Case II.—The next case is that of a man who was thirty-four years old in 1934 when we first saw him. He was then in a hospital in Philadelphia suffering from a rheumatic heart lesion. He gave the following history: Scarlet fever at the age of five years, no tonsillitis or other diseases. Although not physically strong, he had been able to participate in athletic sports. He was not in the habit of smoking more than 20 cigarettes a day, but took more alcohol than was wise. For two years he had had shortness of breath and, in the latter part of this period, attacks of asthma which confined him to bed a few times. During the two months before we saw him he developed marked edema, especially of the legs and scrotum, his abdomen became distended, his liver increased to an enormous size, and he suffered so greatly from dyspnea that rest at night was impossible.

Physical examination revealed a blood pressure of 210/10. The urine showed traces of albumin. There were two murmurs over the heart. The Wassermann reaction was negative.

The patient's physician had discontinued digitalis because it gave no relief but, instead, nauseated the patient. We recommended digitalis lanata suppositories, salyrgan intramuscularly, and advised a thorough examination of the tonsils and a blood count. After a month the family physician reported, "The patient is greatly improved. The edema is a symptom of the past. The tonsils have been cleanly removed and without incident."

When the patient came to us for examination, not long after this, he had lost 25 pounds. His blood pressure was 190/100. Roentgenograms showed a typical aortic-shaped heart and a great increase in the depth of the heart in the lateral film (dilated auricles). The ECG showed low voltage of R I, inverted T I, and an inverted T s (T of lead CR 5). Under digitalis suppositories (twice daily) the patient improved. The blood pressure went down to 160/90 and the pulse rate to 72.

Six months later the patient returned, complaining that his condition was very much worse. He had stopped taking medicine. Three weeks rest, two of which were spent in bed, and the taking of digitalis suppositories twice daily brought about improvement, but three months later the patient returned from a sea voyage in a completely decompensated condition. His liver was very large and his heart was fibrillating. His blood pressure had risen to 230/190. Hospitalization was necessary.

Strophanthin by rectum was now recommended and he was given 1 mg. of strophanthin by rectum twice daily, 1 gm. of diuretin twice daily, and an injection of salyrgan once weekly. Within two weeks his blood pressure dropped to 170/110 and he was discharged. His weight had decreased from 143 to 136 pounds and his general condition was very much better.

At the end of two months he was again in the hospital. Overexertion had brought on a state of complete decompensation. He was admitted with a temperature of 102.5° F. of unknown cause. His blood picture was normal

and his teeth were in good condition. We felt very little hope for recovery. Nevertheless, very slowly the gallop rhythm disappeared and the liver returned to its normal size. At the end of five months he was discharged to his home. While in the hospital he was given, in the beginning, morphine three times daily, and camphor in oil six times daily. This was then reduced to twice daily, and eventually once daily he was given 1 gm. diuretin and once a week salyrgan or mercupurin. Various types of digitalis preparations were tried, but always failed or could not be tolerated. Scillaren was also tried with a similar result. Strophanthin was given intravenously for a short time. When the patient's condition improved this was discontinued in favor of 1/100 grain strophanthin by rectum three times daily.

After his discharge from the hospital the patient remained at home for several months. Then he went to the country accompanied by a nurse. During all that time he continued to take strophanthin by rectum, 1/100 grain twice daily, 1 gm. diuretin, and for several months he received mercupurin or salyrgan once a week, which produced a surplus urine elimination of 1 to 4 liters. Finally, in 1937, he went to Florida and felt fine there for four months. Then his condition changed for the worse. An abscessed tooth was detected and he entered a hospital for its extraction. His physician then forbade strophanthin treatment "because," as he put it, "the heart was already big enough." As soon as possible the patient left the hospital and returned to New York.

We prescribed strophanthin by rectum (1/100 grain twice daily) and the other treatment as before. The condition improved very quickly. Since then the patient has followed the prescribed treatment faithfully. He now feels excellent, his blood pressure is 180/120, his liver is much smaller, he has no congestion of the lungs and his heart appears, even in the lateral view, to have greatly diminished in size. The present weight of the patient, who is 5 feet 7½ inches in height, is 117 pounds. He is able to carry on a moderate amount of work without untoward affect.

Case III.—This case is one of stenocardial distress of frequent occurrence. When first seen in 1937 at the request of Dr. S. K., the patient was sixty-eight years old. Her history was as follows: Three children, cessation of menses at forty-seven, hysterectomy performed at fifty-four. Four weeks previously she had experienced her first attack of angina pectoris. It occurred early in the morning and was followed by a rise of temperature. Her pulse was 120. The initial attack was followed in the next few weeks by six lighter attacks, with associated tachycardia and a rise in blood pressure from 130 to 200 systolic.

At the time of our examination ECG showed distinct changes; there was an inversion of T in all leads, also in the left and right ECG (CR 5 and CR 2), low voltage, especially of the left ECG.

Diuretin and other preparations of the xanthine group were prescribed, as well as luminal and, later, small doses of digitalis leaves; but this treatment failed to improve the patient's condition. The mild attacks of angina pectoris continued to recur. Rectal strophanthin therapy was therefore instituted. Within six months the patient had so greatly improved that she was able to go abroad. The electrocardiogram showed only a flat T. She continued her

strophanthin by rectum while abroad and was in good health on her return. She still continues this treatment and her condition is still excellent.

Case IV.—This patient suffered from heart block. We examined him in 1936 for the first time. He was then fifty-one years old. As a child of three and one-half years he had had pleurisy and was operated on for empyema. His tonsils were removed in 1904. During the World War he was wounded three times. Two years ago he had an attack of sciatica (slight rheumatic fever?). Following that he underwent an operation on his nose.

At about this time he became very busy in the organization of a new enterprise and for recreation made many excursions to a high altitude. After awhile he began to notice that he could no longer walk up hill and that from time to time a black curtain descended before his eyes. He experienced slight attacks of Adams-Stokes syndrome, and his pulse rate dropped to 36. He was treated by a physician for six months, during which his urine, blood and Wassermann tests were all negative.

When he came under our care in 1936 his blood pressure was 180/120 and he was suffering from complete heart block. His pulse varied between 24 and 35 and there was a systolic murmur. The R wave of the (CR₄) right ECG. was deformed. The heart was very much enlarged and horizontally situated. The aorta was fairly normal in size. There was slight congestion in the lungs. Lateral roentgenograms showed highly dilated auricles. All other examinations were negative.

No treatment whatever, including digitalis, influenced the condition until we instituted intravenous strophanthin therapy, beginning with very small doses. Within six weeks the patient lost his stenocardial distress. An abscessed tooth was then discovered and extracted. This infection and the overstraining of the heart with excessive mountain climbing probably account for the heart block. Following removal of the tooth, he discontinued the strophanthin treatment.

A year later his stenocardial distress returned in a more aggravated form. Strophanthin treatment was reinstituted and the patient became free of subjective complaints. His condition has continued like this up to the present. He has been able to resume his work. His pulse rate, however, still varies from 34 to 40 per minute.

This case is presented to illustrate the fact that strophanthin therapy is not contraindicated in the presence of disturbance of the conductive system, namely in complete heart block, but, on the contrary, is very helpful in many instances.

Conclusions.—We have purposely presented only cases in which strophanthin was not administered until after the failure of digitalis therapy. They constitute a very small percentage of the cases in which the results have been similarly successful. If we were to review the hundreds of cases we have treated with strophanthin, we believe the statistical summary would demonstrate the value of strophanthin therapy beyond ques-

tion. Our experience has shown us that strophanthin therapy is superior to treatment with digitalis glucosides: (1) in emergency cases; *(2) in cases of heart failure, especially when the patient has a large and dilated heart;* and, (3), in the treatment of patients with beginning coronary arteriosclerosis. Careful observation of every patient thus treated is imperative. The intravenous administration of doses surpassing 1/100 grain of strophanthin should be avoided so far as possible. Strophanthin therapy in small doses can be continued for a long period without danger of accumulation.

BIBLIOGRAPHY

1. Fraser, Thomas R.: On the Kombé Arrow Poison. Trans. of Anat. and Physiol., **7:** 140, 1872.

2. Fraser, Thomas R.: Strophanthus Hispidus, Its Natural History, Chemistry and Pharmacologie. Trans. of Roy. Soc. Edinburgh, **35:** iv, 955, 1890; **36:** ii, 343, 1891.

3. Kisch, Bruno: Beobachtungen bei einem Kranken mit totalem Block. Cardiologia, ii, 47, 1938.

4. Straub, W.: Ueber Digitaliswirkung am isolierten Vorhof des Frosches. Arch. f. exper. Path., **79:** 19, 1910.

5. Fraenkel, A.: Strophanthintherapie. Berlin, 1933.

6. Cornwall: Strophanthin and Its Therapeutic Use. Medical Record, Jan. 6, 1937.

7. Castaigne, T. de: Practiciens, *32,* 1911.

8. Pribram, H.: Die Digitalistherapie. Verh. 4th Tagung I. D. Ges. f. Kreislaufforschung, 1931.

9. Groedel, Franz M.: Rektale Strophanthintherpie. Ztschr. f. Kreislaufforschung, **27:** 696, 1935.

10. Groedel, Franz M.: The Treatment of Angina Pectoris. New International Clinics, Vol. iv, Series 2, 1939.

11. Eggleston, C.: The Absorption of Strophanthin Following Sublingual and Perlingual Administration. J.A.M.A., **89:** 583, 1927.

CLINIC OF DRS. ABRAHAM LIEBERSON AND A. ALLEN GOLDBLOOM

BETH ISRAEL AND METROPOLITAN HOSPITALS

CLINICAL STUDIES IN ELECTROCARDIOGRAPHY: V. THE VALUE OF CHEST LEADS IN CARDIAC DIAGNOSIS

WHEN Wolferth and Wood[1] introduced the chest lead in the diagnosis of coronary occlusion, an important step forward in the more intimate study of the heart was made. By leading off from the chest wall, which is much closer to the heart than the extremities, we gained new knowledge about the immediately underlying heart muscle that only intimate contact could afford. The later workers in this field, Lieberson and Liberson,[2] Hoffman and DeLong,[3] Katz and Kissin,[4] Goldbloom,[5] Master,[6] etc., helped establish the criteria of what is normal in this lead, and what indicative of heart disease. By an international conference the method of taking the chest lead was finally standardized (according to the original suggestion of one of us[2, 7]), and the chest lead was formally recognized and launched on a useful career. It is interesting now to consider just what rôle it is playing in cardiac diagnosis and what rôle it is destined to play. This is best considered as to its usefulness in:

1. Acute coronary thrombosis.
2. Myocardial disease other than acute coronary closure.
3. As the sole evidence of myocardial disease.

Acute Coronary Thrombosis.—Before we begin to discuss the usefulness of the chest lead in diagnosing acute coronary thrombosis, we must object to the widely circulated belief that coronary thrombosis is essentially an *electrocardiographic* rather than a *clinical* diagnosis. We must therefore stress the limitations of the electrocardiogram (conventional and chest leads) in the diagnosis of this condition. In our recent study[8]

of thirty-four cases of myocardial infarction at Beth Israel Hospital checked at autopsy (sixteen anterior, nine posterior and nine combined anterior and posterior infarcts), eight anterior infarcts, seven posterior infarcts, and only one combined infarct were detected electrocardiographically (47 per cent). The other eighteen cases showed bundle-branch block, or intraventricular block (eleven cases), or nonspecific myocardial damage. In contrast to this, the clinical diagnosis before the electrocardiogram was taken was correct in twenty-six of the thirty-four cases (76 per cent). With both clinical and electrocardiographic study combined, the correct diagnosis was made in 91 per cent of the cases. The primary importance of the *history* and *clinical examination* in the diagnosis of this condition, particularly in patients who are sufferers from old coronary thrombosis or sclerosis, is well illustrated by these figures.

The *chest lead* is evidently most important in diagnosing coronary thrombosis *when the conventional leads are entirely negative.* There is no one who has taken four-lead electrocardiograms in patients with coronary thrombosis who has not come across such a case: the limb leads being negative in all respects, and the fourth lead showing a marked *depression* or elevation of the ST segment, or a deep Q wave indicating an active process occurring in the heart. It is true that if many serial electrocardiograms are taken, the conventional leads in most of these cases would also begin to show some significant changes, such as depression and inversion of the T wave in Leads I and II, but that does not detract from the fact that a precordial lead taken from an area adjacent to an infarct will show characteristic electrocardiographic changes which are neutralized and not detectable in the more distant limb leads. According to some authors, Roth[9] for example, this occurs very infrequently. In the cases reviewed by us at Beth Israel Hospital in the past seven years, the incidence of positive chest leads in the presence of negative limb leads in acute coronary thrombosis is about 4 per cent (Fig. 112 illustrates a typical case).

Less frequently the chest lead assumes major importance in the diagnosis of coronary thrombosis in cases where *changes* in this lead *persist longer than in the conventional leads,* as Gold-

bloom has shown.[10]   In such cases when an electrocardiogram is taken months after the acute closure, the conventional leads may have reverted to normal but the chest lead still remains abnormal and demonstrates a relic of the acute episode, such
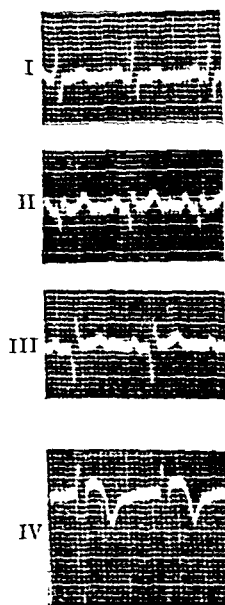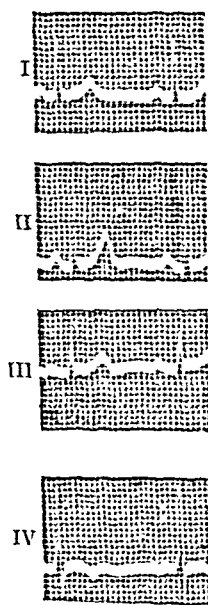
Fig. 112.   Fig. 113.

Fig. 112.—N. B., male, aged sixty-six. Note that although the conventional leads show a deep Q_2 and Q_3 suggesting some degree of myocardial damage, there is no indication that an acute process is occurring in the heart. The chest lead, with its elevated RS-T segment and deeply inverted, coved T wave, indicated the presence of acute coronary occlusion—a diagnosis which the clinical course later justified.

Fig. 113.—S. F., male, aged fifty-four. The conventional leads are within normal limits. The coved, inverted T_4, however, indicates previous coronary damage. Clinically the patient's difficulty began with an attack of precordial pain five months previously from which he did not fully recover. The T_4 changes are apparently the only relic of the acute coronary closure.

as an absent R wave (or inverted T wave). We have encountered several such cases (Fig. 113 is one of these).

Of less absolute importance but frequent in experience is the usefulness of the chest lead in showing the *changes* due to coronary thrombosis *clearly* and *outspokenly*, so that they can

be followed easily and demonstrated with facility to other doctors, medical students, etc.   This is true not only of the QRS changes, where a very prominent Q wave may be demonstrated, but also the marked RST segment changes and the marked peaking and inversion of the T wave.   In the majority of cases of acute coronary thrombosis the chest lead changes are more striking than in the conventional leads (see Fig. 114 for typical
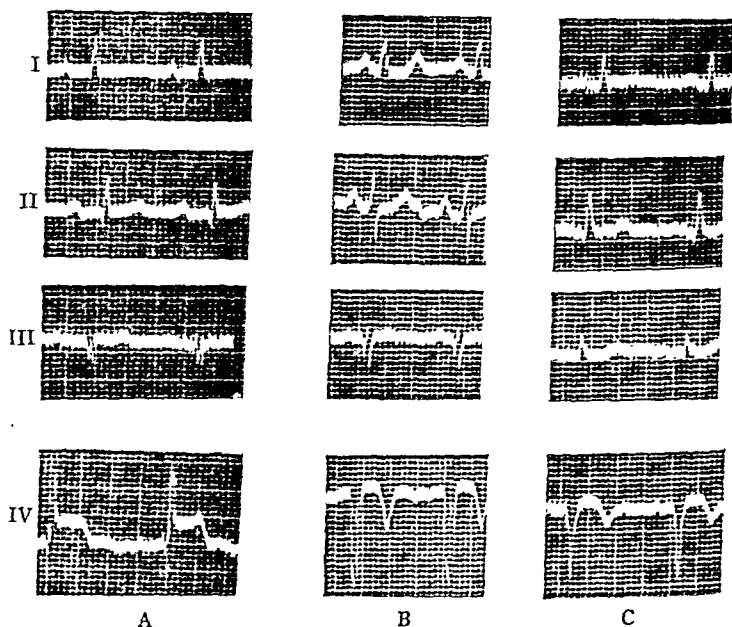
Fig. 114.—Although the conventional leads in the above cases of acute coronary occlusion are not normal, they do not indicate the acuteness of the coronary damage shown by the RS-T elevations and the deeply coved, inverted T waves in the chest leads.

examples).   Only rarely is the opposite true: that the fourth lead changes are less prominent than those of the limb leads (Fig. 115), especially in posterior infarction.

In the electrocardiographic diagnosis of coronary thrombosis a single four-lead electrocardiogram may not indicate acute coronary thrombosis, while *serial* four-lead electrocardiograms may show rapid changes in QRS, RS-T and T wave contours, indicating that an acute process is occurring in the heart.

In our series we[11] have found that the taking of serial four-lead electrocardiograms has increased the accuracy of electrocardiographic diagnosis of acute coronary thrombosis by 4 or 5 per cent, and that the serial changes are apt to occur more often and to be more prominent in the fourth lead than in the limb leads. There was, furthermore, one patient suspected clinically of having suffered a coronary thrombosis who failed to show
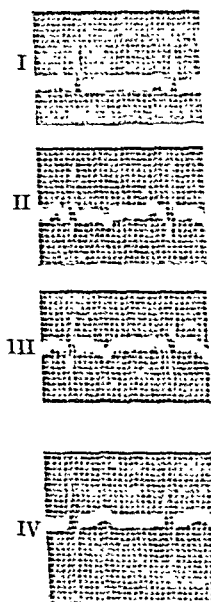
Fig. 115.—I. D., male, aged fifty-three. This illustrates the uncommon condition in acute coronary thrombosis where the conventional leads (with inverted T_2 and T_3, and deep Q_2 and Q_3) are much more abnormal than the chest lead. Note that this failure of the chest lead to register coronary occlusion occurs much oftener with posterior than with anterior infarction.

any deviations from the normal in serial four-lead electrocardiograms when the chest lead was taken from the apical region. When the exploring electrode was placed over several areas of the chest wall (from the sternal border to the left axilla in the fourth interspace), a sudden change in the electrocardiographic contour of the chest lead was noted immediately over the infarcted area (see Fig. 116). In some cases, apparently, there is need for an intensive study of the whole precordium

for corroboration of the clinical diagnosis of acute coronary thrombosis.

In summing up our seven years' experience with the chest lead, we may say that this lead *increases the efficiency of the conventional leads* in detecting and corroborating evidence of acute coronary thrombosis *in about 10 per cent of the cases* if *serial* (and occasionally *multiple*) precordial leads are used; by about 4 or 5 per cent when *single* four-lead electrocardiograms are used.
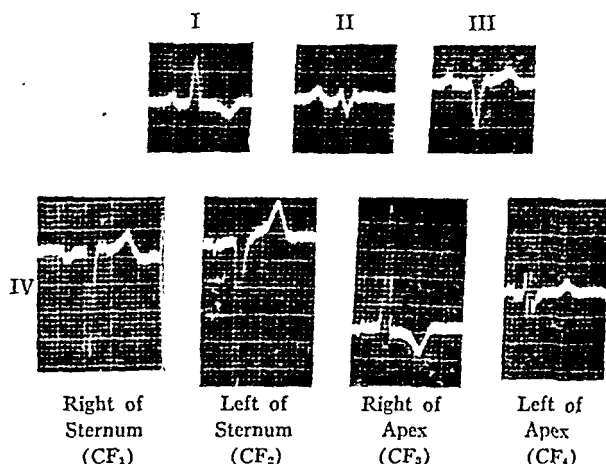
Fig. 116.—P. E., male, aged seventy-four. In the above patient, the clinical history was suggestive of an acute coronary episode a month before an ECG was taken. This showed an inverted T₁, but it was not until several chest leads were taken in the fourth interspace that we found in one localized area (to the right of the apex) a chest tracing markedly different from that of the adjacent area (*i. e.*, a sudden inversion of the T wave), indicating an area of localized damage—an infarction.

Myocardial Disease Other Than Acute Coronary Closure.—Although there is little doubt that the greatest usefulness of the chest leads lies in the diagnosis of the condition for which it was originally introduced (acute coronary thrombosis), it has proved itself of enough value in other conditions to warrant the routine use of the fourth lead in general electrocardiography. It took but little experience with chest leads to realize that these precordial leads are "significant" leads, in which the shape of the QRS, the RST segment, and even the T wave is as

important, if not more so, than in the first and second lead. This corresponds to theoretical considerations that leads taken directly or close to the heart (semi-direct) are more informative, once standardized, than outlying leads.

Thus after a short, trial use of the posterior-anterior chest lead in conjunction with the conventional leads in all cases electrocardiographed at the Marine Hospital, Stapleton, S. I., in 1932, we[2] found it well worth while to establish the four-lead electrocardiogram as routine. The same procedure has applied to Beth Israel Hospital since 1935. In cases in which the standard axial leads are not outspokenly pathologic in border-line cases of myocardial damage, the chest lead is unusually useful in bringing to bear on the problem the findings of another significant lead. Conformity to the normal standards for the new chest lead as we now know it (presence of R wave, diphasic QRS, RST segment not significantly depressed or inverted, upright T wave, except in children, obese or pregnant women) makes us think lightly of any borderline finding in the conventional leads (such as deep Q_3 and inverted T_3). If the fourth lead is abnormal, however, in any or all of the above respects, even minimal changes in the conventional leads assume greater significance and call for further study.

Chest Leads as Sole Evidence of Myocardial Disease. —We finally come to the most important (but rather infrequent) use of the chest leads in general electrocardiography: *i.e.*, as sole electrocardiographic evidence of myocardial disease. We[12] reviewed 4000 four-lead electrocardiograms (3200 cases) at Beth Israel Hospital in the last two years with this point in view: to evaluate the exclusive diagnostic importance of an abnormal precordial lead when the standard leads were normal. The criteria of abnormality adhered to as a basis for this selection were absent R wave, R wave less than 1 mm., QRS of M or W configuration, or inverted T wave in the fourth lead in the presence of normal conventional leads.

Seventy of the 3200 cases showed positive precordial and negative conventional leads. Of these seventy, a group of twenty-three was completely analyzed as representative of the larger group. By careful history, physical examination and x-ray the twenty-three cases with positive chest leads were divided into a cardiac group (57 per cent) and a non-cardiac group

(43 per cent). Among the cardiacs, coronary thrombosis was present only once; while pulmonary disease contributed the greatest number of cases to the non-cardiac group (four out of ten). *Absence of the initial upward deflection (R wave) in Lead IV was the most constant finding in the cardiac group (five out of thirteen cases).* Low R waves occurred with about equal frequency in both groups. Inverted or biphasic T waves were present slightly more often in the non-cardiac than in the cardiac group.

Where the standard leads were normal, the precordial lead was the sole electrocardiographic indicator of heart disease in 1.2 per cent of the 3200 cases studied. An abnormal fourth lead in the presence of normal axial leads was indicative of heart disease in more than 50 per cent of such cases. An absent R wave was of greater significance as a token of myocardial damage than either low R waves or inverted T waves, alone or combined. We thus see that the precordial lead may be the only electrocardiographic evidence of heart disease in conditions other than coronary thrombosis or sclerosis (*i.e.,* 1 per cent of cases).

Summary and Conclusions.—Our seven years' experience with precordial leads confirms our original belief that chest leads have come to stay as an integral part of routine electrocardiography and that the four-lead electrocardiogram should be routine in all cases.

The fourth lead finds its greatest usefulness in the diagnosis of acute coronary thrombosis, where it is positive in about 4 per cent of cases of coronary thrombosis with insignificant findings in the conventional leads. The fourth lead changes are apt to persist longer, and to be the only token of coronary thrombosis in about 2 per cent of the cases. The electrocardiographic changes of coronary thrombosis are more graphically outspoken in the chest lead than the conventional leads, and can be followed serially with greater ease in this derivation. The chest lead is of great use in evaluating borderline findings in the conventional leads, throwing the weight of its evidence either toward or away from a diagnosis of myocardial damage in diseases other than coronary. It has further been found as the sole evidence of myocardial disease in about 1 per cent of cases where the conventional leads were normal.

We therefore not only recommend the four-lead electrocardiogram as routine in hospital practice, but feel that *serial electrocardiography* should be practiced whenever the opportunity presents itself to help determine if any acute process is occurring in the heart, and to raise the accuracy of the electrocardiographic method of determining heart damage. In difficult and borderline cases of myocardial damage (coronary sclerosis, etc.) special studies with multiple precordial derivations from several areas of the heart may be indicated. It is not amiss to state here that in determining the possible presence of infarction at the back of the heart, the *esophageal* lead has been found[13] very useful as a counterpart of the chest lead, simple anatomic considerations indicating that the esophageal lead is to the posterior infarct what the precordial lead is to the anterior infarct.

Keeping in mind the fact that the electrocardiographic method has at best sharp limitations and that it must be constantly interpreted in the light of the clinical findings, the best use is made of electrocardiography by employing serial four-lead electrocardiograms whenever possible, with multiple chest leads or the esophageal lead in difficult cases where special (semi-direct) methods of investigating the cardiac action currents are called for.

BIBLIOGRAPHY

1. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads. Am. J. M. Sc., **183**: 30, 1932.

2. Lieberson, A., and Liberson, F.: The Value of the Posterior-Anterior Chest Lead in Cardiac Diagnosis. Ann. Int. Med., **6**: 1315, 1932–1933.

3. Hoffman, A. M., and DeLong, E.: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage. Arch. Int. Med., **51**: 947, 1933.

4. Katz, L. N., and Kissin, M.: A Study of Lead IV. Am. Heart J., **8**: 595, 1933.

5. Goldbloom, A. A.: Clinical Evaluation of Lead IV (Chest Leads). A Survey of Lead IV in Ambulatory Cases of Coronary Artery Disease and Acute Coronary Occlusion. Am. J. M. Sc., **187**: 489, 1934.

6. Master, A. M.: The Precordial Lead in 104 Normal Adults. Am. Heart J., **9**: 511, 1934.

7. Miscellany: Standardization of Precordial Leads. J.A.M.A., **110**: 395, 1938.

8. Lieberson, A., Chasnoff, J., and Goldbloom, A. A.: Comparative Value

of Clinical and Electrocardiographic Findings in Coronary Thrombosis, as Proved by Autopsy. To be published.

9. Roth, I. R.: Use of Chest Leads in Clinical Electrocardiography. Am. Heart J., 10: 798, 1935.

10. Goldbloom, A. A.: Clinical Studies in Electrocardiography. III. Persistent Abnormal Lead IV Findings in Serial Electrocardiograms with Negative Three Routine Leads, Coronary Thrombosis. Ann. Int. Med., 8: 1404, 1935.

11. Feinstein, M. A., and Lieberson, A.: Characteristic Serial Changes in the Fourth Lead after Acute Coronary Thrombosis. Am. Heart J., 14: 69, 1937.

12. Sussman, R. M., and Lieberson, A.: Fourth Lead Findings as Sole Electrocardiographic Evidence of Myocardial Damage. To be published.

13. Lieberson, A., and Liberson, F.: An Internal Electrocardiographic Lead. Proc. Soc. Exp. Biol. and Med., 31: 441, 1934.

CLINIC OF DR. SAMUEL SILBERT

Mt. Sinai Hospital

VARICOSE VEINS AND VARICOSE ULCERS

THE treatment of varicose veins by the injection method is one of the most notable therapeutic advances in the past decade. The tedious dissections and stripping operations which were formerly employed have now been almost universally discarded. The demonstrated success of the injection treatment in thousands of cases abroad and in this country has resulted in its acceptance by the profession as the method of choice in the treatment of this condition.

Varicose veins are the most important disease of the venous system and one of the most common disorders seen in private and clinic practice. Although the discomfort produced by this condition in any one individual may be minor, the total distress and disability due to varicose veins and its complications is considerable.

Etiology.—The cause of varicose veins is still obscure, but certain points bearing upon the etiology are generally recognized. Since the condition frequently occurs in several members of the same family, both male and female, a *hereditary* factor appears to exist. It is observed with great frequency in women who have had several *pregnancies*. While pressure of the fetus on the pelvic veins may properly be regarded as a contributory cause, it does not entirely explain this association. Varicose veins are frequently noted to develop in the early months of pregnancy, while the uterus is still too small to exert any appreciable pressure. For this reason an endocrine disturbance, most likely of the pituitary gland, is suspected. Standing occupations and the use of circular garters can only be regarded as aggravating factors.

The present tendency is to regard *incompetency of the valves* between the deep and superficial veins as the major cause of varicose veins. The deep veins lie between muscular layers, and the blood in them is propelled upward by the contraction of the muscles. Between the deep and superficial systems, there are numerous communicating veins. Under normal conditions the valves in these veins permit the blood to pass only from the superficial to the deep vessels. When these valves become incompetent, the blood may escape from the deep into the superficial vessels instead of returning toward the heart. The blood thus forced into the superficial veins distends these structures and causes separation of the valve flaps. In this manner venous valves at succeedingly lower levels progressively become incompetent. In the standing position there results a column of almost stagnant blood throughout the course of the superficial veins. It is only by raising the extremity above the horizontal that such veins can be completely emptied of their blood. An understanding of this mechanism explains why it is that, in the erect position, the circulation in varicose veins is reversed in direction.

Diagnosis.—The diagnosis of varicose veins in a typical case is easy. Their usual location is along the course of the greater saphenous distribution on the mesial surface of the thigh and leg. Large veins may also form in the lesser saphenous system on the posterior and lateral sides of the leg. The enlarged tortuous veins are characteristically present in the erect position and promptly disappear when the leg is raised above the horizontal.

It is important to *differentiate* varicose veins from newly formed collateral veins which follow obstruction of the deep venous circulation. When the deep veins have been closed by a previous thrombophlebitis, it will be noted that the extremity is larger and warmer than the opposite side. A degree of cyanosis is usually apparent in the lower leg and foot. The veins which are prominent in the erect position fail to disappear when the extremity is raised to the horizontal. In such cases one should inquire for a history of phlebitis, particularly with relation to operation, childbirth, or febrile illness. Since superficial collateral veins are essential to maintain venous circulation

when the deep vessels are closed, no attempt should be made to obliterate them by injections.

Certain *tests* may be made to determine if the enlarged superficial veins are collateral vessels. If an elastic bandage is applied from the ankle to the knee and the patient is able to walk around for a few hours without pain, the superficial vessels may safely be regarded as not essential for venous return. A second test may be made as follows: The leg is elevated and a tourniquet is placed around the thigh just tightly enough to block superficial venous return. The patient is then allowed to walk. If the superficial veins remain obliterated while walking, the venous return through the deep veins is adequate. Under such circumstances the superficial veins may be closed without danger.

True varicose veins and the signs of a former thrombophlebitis may co-exist in the same patient. For example, an individual who previously had varicose veins might develop a postpartum or postoperative phlebitis. In such a case it will require judgment to decide if the superficial veins are necessary or may be safely obliterated.

When enlarged veins are localized in an area over which there is increased heat, the presence of an *arteriovenous communication* should be suspected. Such an extremity may show considerable enlargement. To establish the diagnosis, samples of blood taken from symmetrically placed enlarged superficial veins are analyzed for oxygen content. If there is an admixture of arterial blood on one side it can readily be recognized by the high oxygen content of the blood.

The *symptoms* of varicose veins are usually mild. Patients may complain of a heavy feeling in the leg, of unusual fatigue, or of some pain. Pain along the course of the veins is frequently aggravated during the menstrual periods. Women are usually more concerned with the unsightly appearance of the leg than by the symptoms produced. Pigmentation and ulceration are frequently seen in neglected cases.

Injection Treatment.—The treatment of varicose veins by the injection method is simple, painless and safe. The ideal sclerosing agent is a fluid which will cause rapid agglutination of the walls of the vein without discomfort. There should be

little danger of a slough if some of the fluid escapes outside of the vein lumen. The solutions previously used, salicylates, sugars, quinine and urea, etc., have gradually been displaced by *sodium morrhuate*. Although this substance has the disadvantage that some patients may be allergic to it, such sensitiveness is relatively rare, and sodium morrhuate is preferred at the present time in most of the large clinics for the treatment of varicose veins.

The *technic* of injection varies considerably. Varicose veins are most prominent when the leg is dependent, and in this position it is easy to insert the needle into the lumen. Many operators prefer to inject the veins with the patient standing. However, there is a serious disadvantage in this method, as clotting of the blood in the distended vein results in unsightly lumps which may require many months to disappear. I prefer to follow the technic suggested by Sicard and Gaugier[1,2] and inject the vein when it is empty: The leg is first placed in the dependent position so that the veins are prominent. The needle is then inserted in the vein and some blood is withdrawn to be certain that the needle is in the lumen. The leg is then carefully raised above the horizontal by an assistant and held in this position until the veins are emptied. The extremity is then lowered almost to the horizontal and the sclerosing solution is injected. When this technic is employed, the internal surfaces of the vein rapidly become agglutinated and there is no clotted blood in the vessel. When the injection is finished and the leg is returned to the dependent position it will be noted that in most instances the vein has completely disappeared.

Because of the possibility of protein sensitivity and the varying individual reaction to injections it is wise to start with a *small dose,* usually 1 cc. If no unusual reaction occurs, the second dose may be 2 cc., and this can be progressively increased to 5 cc. if necessary to obtain satisfactory obliteration. The *frequency* of injections depends upon the extent of the reaction and the amount of disability produced. Usually injections may be given every second or third day. When speed in concluding the treatment is necessary, injections may be given daily and both legs may be treated at each visit. Injections may be made as high in the thigh as 2 inches from the saphen-

ous opening. There need be no fear of producing obliteration of the femoral vein if some of the sclerosing fluid enters it as the blood current is too rapid in this vessel to permit local action to take place.

The most frequent *reaction* following injection consists of a somewhat tender reddened streak along the course of the vein for a distance of 2 to 4 inches. Pain is generally mild or may be absent and the patient may complain only of some stiffness. Rest in bed is unnecessary and undesirable and patients are encouraged to continue about their customary occupations. Occasionally an injection of the usual amount of solution is followed by occlusion of the vein for 6 to 10 inches of its course. There may be marked tenderness and redness associated with rather severe pain. In such cases rest in bed for twenty-four hours and the application of warm epsom salt compresses is generally the only treatment required.

Contraindications to Injection Treatment.—Contraindications to the injection treatment of varicose veins are few. Such treatment should not be given to patients suffering from serious *chronic illness*, or to patients who are *bedridden*. *Sclerotic veins* in old people should not be injected, as such veins are unable to collapse. When advanced *peripheral arterial disease* is present, any surgical procedure in the extremities may initiate ulceration. The state of the peripheral circulation should therefore be determined in all cases before injections are given. It has been stated that varicose veins which appear during *pregnancy* should not be injected as they may disappear after confinement.[2]

When an *acute phlebitis* exists or has been present recently in the superficial veins, it is wise to postpone injections until the inflammatory process has subsided. However, Edwards[3] has reported that he has had no untoward results in patients treated by injections and ligation while acute phlebitis was present. The treatment appeared to have a beneficial effect upon the inflammatory process. He recommends that small doses of the sclerosing agent should be used in such cases as the inflammatory reaction is likely to be severe.

Ligation of Saphenous Vein.—In certain patients with large varicose veins a preliminary ligation of the saphenous

veins in the thighs should be done.[4]   Following this procedure
it will be found that the number of veins which require injec-
tion has been considerably reduced.   It has also been shown
that the tendency to recurrence is greatly diminished by a
preliminary saphenous vein ligation.   Cases suitable for this
procedure are selected by the *Trendelenburg test:* The leg is
elevated to collapse all of the superficial veins.   Pressure is
then made in the thigh over the saphenous vein and the patient
is allowed to stand or place the leg in a dependent position.
Upon release of pressure over the vein the column of blood
can be seen to descend rapidly, distending the vein as it pro-
ceeds downward.   This is called a "positive" Trendelenburg
test.

The *technic of saphenous vein ligation* is relatively simple:
A vertical incision is made on the anterior surface of the thigh
extending from Poupart's ligament downwards a distance of
approximately 3 inches.   The incision should be placed about
one finger's breadth mesial to the femoral pulsation.   The
saphenous vein is found beneath the superficial fascia.   Near
the saphenous opening there are usually two or three large
branches which should be tied.   The vein is then doubly ligated
at the saphenofemoral junction and about 1 inch is resected.
Before closing the distal end, a thin catheter is inserted as far
as it will go and 5 cc. of sodium morrhuate is injected through
it as it is withdrawn.   The operation can be done under local
anesthesia if desired, or under general anesthesia with gas and
oxygen.   *It is inadvisable to attempt this procedure in the phys-
ician's office.*   Unexpected difficulties due to the presence of
large glands or unusual anastomoses may arise and proper
operating room facilities and assistance are desirable.   Patients
may be allowed out of bed on the day after operation, and hos-
pitalization for more than one day is seldom required

Complications.—The complications of varicose veins are
relatively few.   Spontaneous *superficial phlebitis* frequently oc-
curs in such cases, particularly after minor trauma.   The effect
of such a phlebitis is exactly the same as that produced by in-
jections, as it results in an obliteration of the involved veins.
If the attack is mild, bed rest is unnecessary; if it is more
severe, a few days in bed with the extremity elevated and ap-

plication of warm epsom salt compresses usually suffices. As soon as the pain has stopped patients may be allowed to walk.

Emboli from superficial phlebitis in varicose veins are exceedingly rare. The reasons for this are readily apparent. When the patient is upright, the current of blood in the varicose veins is reversed and flows away from the heart. Any loose clot would thus tend to be jammed into the narrower distal portion of the vein. The communicating veins between the deep and superficial venous systems are too small to allow the passage of an embolism of any size. However, it should be remembered that in a patient confined to bed with the legs horizontal the direction of the blood in the varicose veins tends to be toward the heart. Under these circumstances a free clot *of some size could pass through the saphenous vein to the* femoral and cause a pulmonary embolism. *Patients with superficial phlebitis,* whether spontaneous or chemically produced, *are therefore safer if kept ambulatory.* The mechanical obstruction produced by saphenous vein ligation serves as a further safeguard.

Neglected cases of varicose veins show certain changes in the skin of the legs, particularly *pigmentation* and *ulceration.* The almost stagnant or sluggish column of poorly oxygenated blood hinders capillary circulation and gradually results in impairment of the nutrition of the skin. Ulceration is then initiated by some minor trauma. Such ulcers vary in size from ½ inch to 4 or 5 inches. Neglected or extensive ulceration may present difficult surgical problems. *Varicose ulcers* should be *differentiated* from those due to *malignancy, syphilis, tuberculosis* and other infections. The chief differential point is the presence of obvious large varicose veins.

Treatment of Varicose Ulcers.—Most varicose ulcers respond rapidly to *simple treatment:* This should consist of rest with the leg elevated and the application of a wet dressing of warm boric acid to the ulcerated area. When the surface is clean, a cod liver oil ointment frequently expedites healing. Exposure to ultraviolet light is also valuable. When the ulcer is perfectly clean, strapping across the surface with strips of adhesive plaster is followed by rapid healing. Most varicose

ulcers will yield to these simple measures and heal in a few weeks.

Various *ambulatory methods* of treatment of varicose ulcers have been devised for patients who are unable to obtain bed rest: After applying a bland ointment to the ulcer, a thick flat rubber sponge is held in place over it by means of an Ace bandage. The patient is then encouraged to walk and the activity of the muscles results in a better arterial and venous circulation. This is the so-called "sponge heart" method.[5]

The use of semi-rigid *gelatin-zinc bandages* has considerable vogue. This type of bandage is soft when applied but becomes semi-rigid when dry. It is applied directly over the ulcer and is usually left in place for one week to ten days. The disadvantage of this method of treatment is that the secretion from the ulcer is allowed to remain in place for several days. Irritation of the skin and disagreeable odors from the dressing may result.

The use of *iontophoresis* with *mecholyl* in the treatment of varicose ulcers has been advocated.[6] Asbestos paper soaked in 0.5 per cent mecholyl is wrapped around the entire leg, leaving the ulcerated surface exposed. The positive electrode of a galvanic battery is applied to it and a larger indifferent electrode is placed on some other part of the body. Treatments are given for twenty to thirty minutes three times a week. This method is stated to heal many recalcitrant ulcers. The method is relatively expensive and is not needed in the great majority of cases.

The healing of all varicose ulcers is accelerated by injection of the varicose veins. However, it is unwise to begin injections if the ulcer is inflamed and obviously infected. The ulcer should first be treated by rest and warm boric acid wet dressings. When the surface is *clean*, injections of the veins may safely be done. Similar precautions should be employed if saphenous vein ligation is to be undertaken.

Summary.—The simplicity of the injection method of treatment for varicose veins has placed in the hands of the general practitioner an effective means of curing this condition. If the veins are obliterated when they first appear, the late complications, particularly extensive ulceration, can be entirely

prevented. The tendency to recurrence after satisfactory obliteration should be explained to the patient, and she should be requested to return every six months for examination. If recurrences or new varicosities are treated when they first occur, very few treatments are required. With proper care the legs can be kept free of any unsightly bulges or blemishes.

BIBLIOGRAPHY

1. Sicard, J. A., and Gaugier, L.: Treatment of Varices by the Sclerosing Method. Paris, Masson and Cie, 1927.

2. Forestier, J.: Varices of the Lower Limbs. J.A.M.A., 90: 1932 (June) 1928.

3. Edwards, E. A.: Thrombophlebitis of Varicose Veins. Surg., Gynec. and Obstet., 66: 236 (Feb.). 1938.

4. Trendelenburg, F.: Ueber die Unterbindung der Vena Saphena Magna bei Unterschenkelvaricen. Beitr. z. klin. Chir., 7: 195, 1890.

5. McPheeters, H. O., and Merkert, C. E.: Varicose Ulcers. Surg., Gynec. and Obstet., 52: 1164 (June) 1931.

6. Saylor, L., Kovacs, J., Duryee, A. W., and Wright, I.: The Treatment of Chronic Varicose Ulcers. J.A.M.A., 107: 114 (July) 1936.

CLINIC OF DR. MAX SCHNEIDER

SYDENHAM HOSPITAL

THE TREATMENT OF LEUKORRHEA

THE treatment of leukorrhea, which is only a symptom of many diseased conditions, can be greatly simplified if the following outline is visualized:

I. *Age Group:*	*Children*	*Adults*	*Post Menopause*
	Uncleanliness.	Endocervicitis.	Senile vaginitis.
	Foreign body.	Gonorrhea.	Malignancy of
	Gonorrhea.	Pelvic pathology.	genital organs.
		Trichomonas.	Trichomonas.

II. *History:*

    (A) 1. Puberty.

        2. Pre- and post-menstrual.

        3. Postpartum and postabortal.

        4. Menopause.

    (B) Habits: 1. Excessive coitus.

              2. Psychosexual:

                    (a) Masturbation.

                    (b) Repression.

                    (c) Coitus interruptus.

               3. Sedentary occupations.

               4. Constipation.

               5. Irritating chemical douches.

    (C) Associated Medical Conditions:

          1. Anemia.

          2. Vitamin deficiency.

          3. Endocrinopathy.

          4. Malnutrition.

          5. Diabetes.

          6. Cardiac decompensation (venous stasis).

    (D) Associated Genito-urinary Complaints:

          1. Dysuria.

          2. Dyspareunia.

          3. Burning around vulva and thighs.

III. *The Examination:*

    (*A*) Character of discharge:

        1. Color (white, green, yellow, bloody).

        2. Odor.

        3. Purulent.

        4. Frothy.

        5. Watery.

    (*B*) *Origin of discharge (anatomic diagnosis):*

        1. External genitalia.

            (*a*) Skenetis.

            (*b*) Bartholinitis.

            (*c*) Vulvitis.

        2. Vagina.

            (*a*) Gaping introitus.

                1. Lacerated perineum.

                2. Cystorectocele.

                3. Prolapsus.

            (*b*) Ulceration of vaginal mucosa.

                1. Foreign body.

            (*c*) Moniliasis.

                1. Foreign body.

        3. Cervix (endocervicitis).

            (*a*) Specific—gonorrheal.

            (*b*) Nonspecific—laceration and infection.

            (*c*) Erosion.

        4. Pelvic pathology.

            (*a*) Malpositions of uterus.

            (*b*) Tumors of uterus and adnexa.

            (*c*) Chronic pelvic infection.

    (*C*) Slide diagnosis (infectious etiology):

Wet Smear	*Stained Smear*
(hanging drop)	1. Gonorrhea.
1. Trichomonas.	2. Amount of pus cells.
2. Moniliasis.	3. Character of epithelial cells (estrogenic deficiency).
	4. Other bacteria (Doederlein's).

The first division in the outline is labeled *Age Group*. As the patient presents herself, the physician almost automatically thinks of the few most common causes of leukorrhea for each age group (as outlined).

Many gynecologists have stated that the *history* is of secondary importance to the pelvic examination. This does not hold true of leukorrhea, because it is a symptom of many different conditions; it is the objective expression of a diseased

state which may be organic or functional. It may, however, also be a physiologic increase of the normal vaginal discharge. Emphasis must be placed upon the normal increase in vaginal discharge occurring at certain times, as mentioned in IIA, and the importance of bad habits in the causation of this condition.

At this point, one should note that individuals vary in their *sensitivity* to vaginal discharge. In the gynecologic clinics one sees many women with profuse mucopurulent discharge for which no treatment is sought or any complaint made. On the other hand, in private practice, patients will often seek relief for only a slight increase in a mucoid discharge occurring before and after the menses.

A general *physical* and *laboratory examination* is as important in the diagnosis of the cause of leukorrhea as in any other complaint. Thus anemia and diabetes and malnutrition may be discovered as causes of unexplained vaginal discharge.

The first observation in the local examination is the *character of the discharge*, which will often give a clue to the etiology. A *mucoid* discharge (verified on slide examination by lack of pus cells) will rule out an infective process and point to an increased physiologic secretion or to local pelvic congestion. A *frothy* discharge will make one think of a Trichomonas infestation. A *foul, odorous, scrosanguineous* discharge should make one suspect a malignant process. *Gonorrheal* discharges are always thick and pussy. A *whitish thick* discharge may be due to an increase in the desquamation of the vaginal mucosa. A *thin, watery* leukorrhea is the common finding in senile vaginitis.

The *anatomic diagnosis*, or origin of the leukorrhea, is the next step. This is of the utmost importance in the establishment of a permanent cure. Thus, unless one removes the foci of infection in Skene's or the Bartholin glands, there will be recurrence of the discharge after an apparent cure. The pelvic congestion resulting from the venous stasis accompanying a pelvic tumor, a retroverted uterus, or a chronic pelvic infection will cause a persistence of the discharge in spite of all local treatment.

After the general physical and local examination, there follows the necessary *laboratory tests;* a *hemoglobin* and *red blood*

III. *The Examination:*

    (*A*) Character of discharge:

        1. Color (white, green, yellow, bloody).

        2. Odor.

        3. Purulent.

        4. Frothy.

        5. Watery.

    (*B*) Origin of discharge (anatomic diagnosis):

        1. External genitalia.

            (*a*) Skenetis.

            (*b*) Bartholinitis.

            (*c*) Vulvitis.

        2. Vagina.

            (*a*) Gaping introitus.

                1. Lacerated perineum.

                2. Cystorectocele.

                3. Prolapsus.

            (*b*) Ulceration of vaginal mucosa.

                1. Foreign body.

            (*c*) Moniliasis.

                1. Foreign body.

        3. Cervix (endocervicitis).

            (*a*) Specific—gonorrheal.

            (*b*) Nonspecific—laceration and infection.

            (*c*) Erosion.

        4. Pelvic pathology.

            (*a*) Malpositions of uterus.

            (*b*) Tumors of uterus and adnexa.

            (*c*) Chronic pelvic infection.

    (*C*) Slide diagnosis (infectious etiology):

Wet Smear	*Stained Smear*
(hanging drop)	1. Gonorrhea.
1. Trichomonas.	2. Amount of pus cells.
2. Moniliasis.	3. Character of epithelial cells (estrogenic deficiency).
	4. Other bacteria (Doederlein's).

The first division in the outline is labeled *Age Group.* As the patient presents herself, the physician almost automatically thinks of the few most common causes of leukorrhea for each age group (as outlined).

Many gynecologists have stated that the *history* is of secondary importance to the pelvic examination. This does not hold true of leukorrhea, because it is a symptom of many different conditions; it is the objective expression of a diseased

state which may be organic or functional. It may, however, also be a physiologic increase of the normal vaginal discharge. Emphasis must be placed upon the normal increase in vaginal discharge occurring at certain times, as mentioned in II*A*, and the importance of bad habits in the causation of this condition.

At this point, one should note that individuals vary in their *sensitivity* to vaginal discharge. In the gynecologic clinics one sees many women with profuse mucopurulent discharge for which no treatment is sought or any complaint made. On the other hand, in private practice, patients will often seek relief for only a slight increase in a mucoid discharge occurring before and after the menses.

A general *physical* and *laboratory examination* is as important in the diagnosis of the cause of leukorrhea as in any other complaint. Thus anemia and diabetes and malnutrition may be discovered as causes of unexplained vaginal discharge.

The first observation in the local examination is the *character of the discharge,* which will often give a clue to the etiology. A *mucoid* discharge (verified on slide examination by lack of pus cells) will rule out an infective process and point to an increased physiologic secretion or to local pelvic congestion. A *frothy* discharge will make one think of a Trichomonas infestation. A *foul, odorous, scrosanguineous* discharge should make one suspect a malignant process. *Gonorrheal* discharges are always thick and pussy. A *whitish thick* discharge may be due to an increase in the desquamation of the vaginal mucosa. A *thin, watery* leukorrhea is the common finding in senile vaginitis.

The *anatomic diagnosis,* or origin of the leukorrhea, is the next step. This is of the utmost importance in the establishment of a permanent cure. Thus, unless one removes the foci of infection in Skene's or the Bartholin glands, there will be recurrence of the discharge after an apparent cure. The pelvic congestion resulting from the venous stasis accompanying a pelvic tumor, a retroverted uterus, or a chronic pelvic infection will cause a persistence of the discharge in spite of all local treatment.

After the general physical and local examination, there follows the necessary *laboratory tests;* a *hemoglobin* and *red blood*

cell count to rule out anemia; a test for *sugar in the urine;* a *wet smear test* (normal saline) for Trichomonas and yeast organisms; a *stained smear* for gonococci and moniliasis. In the *slide test* it is important to notice the amount of pus present, which will indicate the amount of infection present. The *carbolfuchsin smear* for study of the epithelial cells as an aid to estimate the estrogenic activity is one of the newer tests.[1] The pH of the vaginal secretion is another aid in determining the normality of the vaginal secretion.[2]

Treatment.—With the above outline, the treatment of leukorrhea is easily allocated to the etiologic and anatomic factors.

A *physiologic increase in the normal discharge,* occurring at the menses or at puberty, of course needs no treatment. An explanation of the reason for this discharge may be all that is necessary. If the patient is very sensitive to the increased wetness, or perhaps is irritated in hot weather, a simple astringent douche with a teaspoon of a powder containing equal parts of alum, tannic acid and boric acid may be sufficient to relieve her. However, it is important to warn her to douche only when the discharge is causing discomfort and not to develop the habit of douching. In these cases the dry treatment is often very efficacious. The latter consists of insufflating a mixture containing equal parts of Kaolin and sodium bicarbonate into the vagina by means of a powder blower. Another method is to insert a tampon of Boroglycerin twice weekly for a few weeks, with the patient using the astringent douche on the intervening days.

When the discharge is caused by *bad habits,* the correction of these will of course cure the symptom. But it is well to advise the patient to use an astringent douche for a few weeks or to give her the dry powder treatment until the discharge disappears. The above treatment can be applied to the leukorrhea accompanying a medical condition. It will afford the patient considerable relief, but it will undoubtedly recur unless the medical condition is cured.

Leukorrhea resulting from *pelvic pathology* of course necessitates the treatment of the specific lesion.

Endocervicitis and *erosion* are best treated by electric cau-

tery or coagulation. In our hands, the electrocautery method, as advocated by Dr. Dickinson,[3] has been found the simplest and most satisfactory. In consists in making linear stripes or punctures with the fine nasal cautery tip in the diseased cervix. Such treatment should be given only a week after the menses and when there are no signs of any pelvic inflammatory process in the adnexa or parametrial areas. After the treatment it is well to advise the patient to stay in bed for two days. When the erosion is extensive, it is best not to cauterize completely at one treatment but to repeat every two months.

This brings us to the treatment of leukorrhea caused by specific conditions:

Gonorrhea.—Smears may be negative although, clinically, the presence of urethritis, Bartholinitis, or Skenetis, and a greenish pussy discharge, may point toward a previous or present infection. When possible, *cultures* should be taken, as it has been shown that the latter prove the diagnosis of gonorrhea more often than the slide examinations. Cultures, however, must be made with a special medium. The active local treatment of a gonorrheal infection has been given up by most gynecologists. Rest, physical and sexual, and the use of sulfanilamide, are now the established methods of treatment. Dr. Long[4] recommends the following *sulfanilamide routine* (with variations according to size and weight of patient):

Days			
Days	1 and 2	80 grains	
"	3–4–5–6	60 "	four equal daily doses
"	7 to 14	40 "	
"	14 to 28	20 "	

Sixty grains of sodium bicarbonate are given twice daily.
Patient to be seen daily for the first week.
A daily hemoglobin for the first week; white blood count every other day.
Patient to be examined pelvically and slides made once a week.
A low pressure, warm potassium permanganate douche may be given daily when there is an irritating discharge.

Trichomonas.—Whether Trichomonas is really the causative etiologic agent in a vaginitis characterized by a green frothy discharge and an inflamed vaginal mucosa has not been accepted by many authorities. Some claim that there are other

bacteria, such as streptococci, which cause the inflammatory condition.

If the patient has had *no previous treatment,* I have used a very simple method: She is advised to make, twice daily, lukewarm douches, using 4 tablespoonsful of vinegar to 2 quarts of water. If there is a great deal of vaginal irritation, I recommend the astringent douche mentioned previously. These douches are continued for about three months. They give immediate relief and usually cure the vaginitis. Iron and vitamins are also prescribed and the patient is ordered to have sufficient rest and fresh air and to avoid any sexual intercourse. It is important to emphasize that the mere presence of Trichomonas on slide examination does not mean that any treatments are to be given unless there are complaints of vaginitis.

If the leukorrhea is *persistent* and *recurrent,* the following routine is recommended:

For the first two weeks—Office treatment:
1. Dry vagina gently but thoroughly.
2. Insufflate with powder blower through a vaginal speculum, a powder containing beta lactose.
3. Repeat daily for two weeks.

The patient douches every morning with 2 quarts of lukewarm water containing 1 teaspoonful of lactic acid. (This removes the powder insufflated on the previous day.) Douching is continued throughout the menstrual period.

For the following three months: The patient inserts, every night, ½ to 1 ounce of beta lactose in a veterinarian capsule (top of cap should be removed). This regimen must be followed. The powder insufflations are made a few days before and after the menses. General supportive treatment should also be given. If the vaginitis recurs, the husband should be examined as a possible carrier of the Trichomonas. If that is impossible, condoms during coitus may be tried.

Moniliasis (yeast infections).—For yeast infections, painting the vagina with 1 per cent gentian violet for five successive days has been found to be very effective. The patient also douches with lukewarm water containing 1 teaspoonful of tincture of iodine for the following month.

Senile vaginitis.—The senile vaginitis cases have responded

very well to estrogenic suppositories (2000 I.U.).[5] These are inserted every night for one month, and the patient douches every morning with a mild astringent solution. The results of this treatment can be easily followed by use of the carbolfuchsin smears (Papanicolaou[1]).

Vaginitis in children.—This is either specific (gonorrheal) or nonspecific. In the latter instance, if no foreign body is present in the vagina, uncleanliness is probably the most important etiologic factor. The mother is advised to bathe the child daily, washing the vulva with tincture of green soap, but no vaginal instillations or irrigations are to be used. If this treatment is not successful (which is seldom the case), the use of estrogenic suppositories is advocated. For *gonorrheal* vaginitis in children, very good results are obtained by use of the estrogenic suppositories as outlined below:

1. Wash vulva at bath.
2. Insert, at night, an estrogenic suppository containing 1000 I.U.
3. Take smears weekly.
4. After the first negative smear, repeat for two more weeks.
5. If weekly smears continue negative, stop treatment.
6. The average patient is cured in one month.

BIBLIOGRAPHY

1. Papanicolaou, Geo. N., and Shorr, Ephraim: The Action of Ovarian Follicular Hormone in the Menopause. as Indicated by Vaginal Smears. Amer. Jour. Obstet. and Gynecology. **31**: 806 (May) 1936.

2. Lewis, R. M., and Weinstein, Louis: The Production of Vaginal Acidity by Estrin. Surg., Gynec. and Obstet., **63**: 640 (Nov.) 1936.

3. Dickinson, Robert L.: Endocervicitis and Eversion and the Nasal Cautery Tip. Amer. Jour. Obstet. and Gynec., **2**: 600 (Dec.) 1921.

4. Long: Med. Clin. N. A., Vol. 23, No. 2, p. 345 (March) 1939.

5. Davis, M. Edw: Surg., Gynec. and Obstet., **61**: 680 (Nov.) 1935.

CLINIC OF DR. DAVID SCHERF

FLOWER AND FIFTH AVENUE HOSPITALS

THE CIRCULATION AND HYPOÖVARIANISM

THE general diagnostic and therapeutic problem presented by the climacteric female is such an ordinary experience in the daily practice of medicine that its complexity and protean character is universally recognized. Moreover, the participation of various anatomic systems, as evidenced by a variety of symptoms, is also thoroughly appreciated. In this connection one may recall the terms "menopausal neurosis," "menopausal arthritis," etc. Accordingly, it might be anticipated that the *cardiovascular* system would also show involvement and that symptomatic expressions of the climacterium might at times dominate the clinical picture. However, if textbooks of medicine may be employed as criteria, this situation does not prevail. Many exhaustive treatises dismiss the subject with a few words, and others do not mention it at all.

This situation stands in sharp contrast to the fact that approximately 20 per cent of the female patients seen in the private practice of a cardiologist have complaints which may legitimately be attributed to disturbances of ovarian function. Moreover the symptoms often are not merely *incidental* annoyances, but they may be very prominent and lead to diagnostic and therapeutic errors of considerable consequence. This neglect of a special problem within the broader field is not peculiar to the cardiac aspect of the climacterium. The *respiratory* system, whose disturbance is reflected in sighing respiration (the sigh of relief!), presents an extremely suggestive symptom of great diagnostic value and which likewise has been neglected. Without intending to minimize the importance of other phases of the climacterium nor to magnify the rôle of the heart, it has seemed advisable to limit the pres-

ent discussion to a consideration of some practical diagnostic and therapeutic problems related to the cardiac domain.

Underestimating the Symptoms.—If a female patient, about forty-five years of age, complains of *shortness of breath, palpitation* and *pain* in the *cardiac* region and also notices irregularities of her menstruation, her physician naturally and correctly attributes her symptoms to the climacterium. He feels more confident of his diagnosis if *hot flushes, splitting headache, paresthesias* and *vertigo* appear. Great emotional instability and irritability frequently co-exist; the patient has complaints everywhere. Since the examination does not reveal any abnormality except tachycardia and cardiac hyperexcitability, the diagnosis of climacteric neurosis or neurocirculatory asthenia in a climacteric individual seems to be justified and is readily accepted. The patient is often treated with bromides and phenobarbital, and *after months or years of distress the symptoms gradually subside.*

As a matter of fact, however, these patients are not merely *"neurotic,"* since recently *objective* findings have been discovered which indicate that severe changes occur in the cardiovascular system. Accordingly the actual status of these patients is often incorrectly appraised and the *seriousness* of their symptoms *underestimated*. The readiness with which their distress has been assigned to a "neurosis" or to "neurocirculatory asthenia" is partly responsible for the general unawareness of the true import of the symptoms and to the neglect of cardiac participation.

Overestimating the Symptoms.—Not less frequently a woman who seeks relief, relates the symptoms mentioned above with great tranquillity. Examination reveals dilatation of the heart, especially of the left ventricle, a rough systolic murmur over the apex or the aorta, and a tachycardia and hypertension of 220/110 mm. of Hg.; if the electrocardiogram shows evidence of a "myocardial lesion" the diagnosis of hypertensive heart disease with coronary sclerosis or angina pectoris is common. Corresponding treatment with considerable restriction upon the activity of the patient is initiated. The prognosis seems grave. Nevertheless, we know today that in this group of patients the *seriousness* of the situation has often been greatly *overestimated* in the past. We are now able to relieve

the symptoms or to restore the health of such patients within a relatively short time. Accordingly mistakes in both directions, under- and overemphasis, are committed.

Electrocardiographic Evaluation of Patient's Circulatory System.—This advancement of knowledge in respect to the circulatory system of climacteric patients was made possible by a study of their electrocardiograms. These tracings may show alterations which are known to constitute signs of myocardial damage. Treatment with *estrogenic hormone* re-
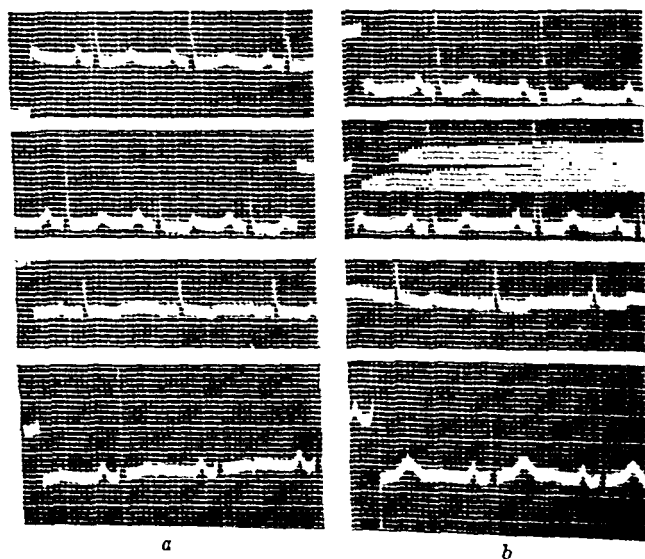
Fig. 117.—Showing effect of estrogenic hormone on the electrocardiogram: *a*, before, and *b*, after treatment.

sults in the return of the normal electrocardiogram within a short time.

Fig. 117, for example, shows the electrocardiogram of a forty-year-old woman whose tubes and ovaries had been resected seven years earlier. She complained of palpitation and chest pain independent of effort. Physical examination and x-ray of the heart yielded normal findings. The blood pressure was 160/105 mm. of Hg. The electrocardiogram (Fig. 117, *a*) shows a sinus tachycardia with a rate of 88. The initial complex is normal in each lead. The T-waves are abnormally low

in Leads I and II. The T-wave in Lead III is inverted; in the chest lead (right arm to left lower parasternal region) it is biphasic and very low. The S-T segment in Lead II is depressed.

The patient was treated with estrogenic hormone, one capsule containing 2000 units daily for nine days. In spite of this small dose the patient felt marked improvement. The blood pressure fell to 140/90 mm. of Hg. The heart rate on the tenth day was 75 (Fig. 117, *b*). In Leads I and II the T-waves were higher, and their negativity in Lead III disappeared. In the chest lead a high positive T-wave was present. The depression of the S-T segment in Lead II has diminished markedly.

The alterations in the electrocardiogram of such patients usually consist in a *depression of the S-T segment,* most decided in Lead II, and a *lowering* or rarely *inversion* of the *T-waves.* The initial complex is not affected; rarely, a slight prolongation of the P-R interval appears. These alterations are by no means, however, characteristic; they are found in a great variety of diffuse myocardial lesions. One must also be careful to exclude previous treatment with *digitalis;* the depression of the S-T segment due to digitalis, however, is usually of a different type and exhibits a slow descent and a rather steep ascent to the iso-electric line.

' It is not permissible, however, to diagnose a *"climacteric heart"* by the electrocardiogram alone. Frequently a myocardial lesion of some other type cannot be eliminated without observation for some time. However, the following facts prove that these alterations of the electrocardiogram in the group under discussion are due to the diminished formation of female sex hormone. Treatment of these patients by means of rest in bed and with various vasodilators for weeks is not followed by a change of the electrocardiogram. On the other hand, the administration of *estrogenic hormone* provides relief of the symptoms and the electrocardiogram is normalized within one to three weeks. If the treatment is interrupted, the former alteration of the electrocardiogram frequently reappears after a variable time.

The changes in the electrocardiogram are *not* dependent upon the *hyperthyroidism* that is frequently encountered in the

climacterium. The alteration of the final deflection may be present without an elevation of the blood pressure; moreover, the typical alterations ordinarily found in hypertension are quite different from those described above.

Fig. 118 was obtained from a forty-year-old woman with uterine fibroids; she had been sterilized by x-ray therapy three months earlier. Splitting headache, numbness in the left arm, precordial pain, independent from effort, were her chief complaints. The blood pressure was 213/130 mm. of Hg.
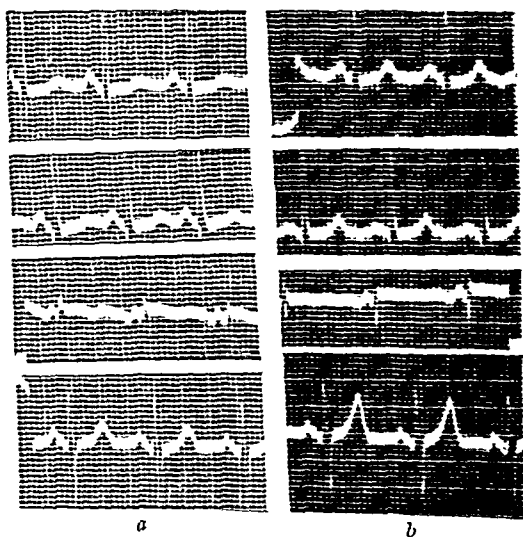
Fig. 118.—a, Before, and b, after treatment.

The electrocardiogram (Fig. 118, a) shows changes similar to those of Fig. 117, a. The rate is increased to 96; the S-T segment is depressed in Leads I and II, and the T-waves are positive but abnormally low in the same leads. In Lead III, the S-T segment is slightly elevated and the T is inverted. After five intramuscular injections of 5000 units of estrogenic hormone within a period of eleven days the rate amounted to 88 (Fig. 118, b). The S-segment and the T-waves have become normal in each lead; the T-wave in the chest lead is higher. The blood pressure had fallen to 180/110.

The alterations of the electrocardiogram described do not only appear in the natural or artificial climacterium. They are

also found in *young patients* with ovarian insufficiency, especially in patients with *hypogenitalism* and *hypoövarianism*.

Fig. 119 was obtained from a twenty-two-year-old woman who suffered from irregular menstrual periods, hot flushes, pressure in the precordial region, and palpitation.

The electrocardiogram in Fig. 119, *a* shows a rate of 110; the S-T segment in Leads I, II and the chest lead is depressed under the iso-electric line; the T in Lead III is inverted. After six injections of anterior hypophysis hormone (gonadotropic) the patient felt much improved. The electrocardio-
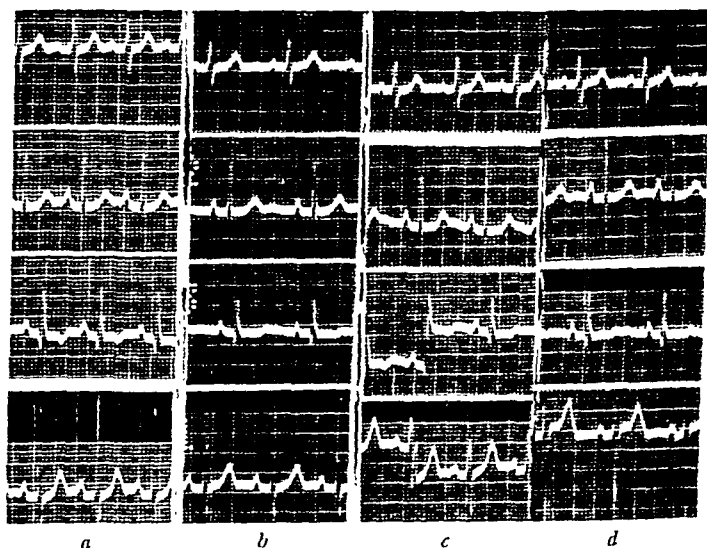
Fig. 119.—Showing effect of gonadotropic hormone on the electrocardiogram.

gram (Fig. 119, *b*) became normal. The pulse rate is reduced to 83, the S-T segment is in the iso-electric line, and the T-wave is normal. Treatment was then interrupted. Two months later the patient returned with the original complaints: the electrocardiogram (Fig. 119, *c*) shows again a tachycardia of 96 beats per minute and the former alterations of the final deflection, although they had not reached the extent shown in Fig. 119, *a*.

Then a new series of six injections of anterior hypophysis hormone was given within a period of three weeks. They fur-

nished the same relief as the first series. The electrocardiogram taken two days after the last injection (Fig. 119, *d*) again shows normal ventricular complexes with a rate of 85.

Confusion in Terminology.—The alterations of the electrocardiogram described may be found in any woman between the ages of fifteen and seventy years whose ovarian function is disturbed. Therefore it is better not to call them *"menopausal changes."* Just as the flushes, the hypertension and other disturbances the electrocardiographic signs as well may appear years before or many years after the menopause. The so-called "menopausal disturbances" and the menopause may coincide in time, but frequently *years* elapse between them. The term *"climacteric"* also cannot be recommended because it is frequently employed wrongly as a synonym to "menopausal."

The term *"climacteric disturbance"* is reserved for phenomena connected with the physiologic or artificial cessation of ovarian function. The same syndrome may appear, however, as the result of ovarian *underfunction,* years before, in young patients still menstruating. When a physician explains to the patient that her complaints are caused by the "change of life," he may receive the indignant answer: "It is impossible! I am too young and my menstruation is still normal." In another case the patient informs the physician: "No, doctor, you are wrong. I am an old woman and have not menstruated for many years." It might be anticipated that the laity would associate the symptoms described with the menopause, but this ought not occur among physicians.

Endocrine Imbalance.—Since it is known that hot flushes and other symptoms may appear at a time when considerable quantities of estrogenic hormone are still found in the blood and urine of the patient, and since so many patients do not develop any symptom even after bilateral oöphorectomy, one may assume that the *deficiency of estrogenic hormone is not solely responsible for the phenomena described.*

Imbalance of the endocrine glands is the *chief factor.* Whether this imbalance is caused only by the diminished formation of estrogen is still not completely answered. Corresponding to the status of the endocrine glands and of the autonomic nervous system, the reaction of the individual patient will vary decidedly: Some patients develop a hyperten-

sion, some cardiac phenomena, some only vasomotor symptoms, and others mainly signs of hyper- or hypothyroidism, etc. In different countries the frequency of the single reactions differs; the race of the patient also seems to play an important rôle. Therefore it is clear that statistics vary in regard to the incidence of symptoms.

The same disorder in the endocrine system, and therefore the same alterations, may occasionally be found without a disturbance of the ovarian function.

It is still undetermined whether, as a result of the endocrine imbalance, a *primary alteration* of the tissues causes the abnormal electrocardiogram, or whether a disturbance of *myocardial blood supply* is responsible. The facts, which tend to support the latter possibility, are discussed elsewhere. Some studies seem to indicate that estrogenic hormone is a vasodilator. We know that constriction of peripheral vessels may occur when the formation of estrogenic hormone is inadequate, and it is possible that the endocrine imbalance observed in such women may cause an increased activity of the heart, without a corresponding increase of blood supply. Thus the S-T segment and the T-wave may become abnormal.

Cardiac Alterations in Patients with Ovarian Dysfunction.—The knowledge of the cardiac alterations in patients with an ovarian dys- or hypo-function will facilitate our understanding of many conditions and influence our medical management.

In many articles which deal with the *pain* in the *precordial area* in climacteric patients and its differentiation from a true anginal pain, it is emphasized that the differentiation is possible by the electrocardiogram, since this is abnormal only in patients with angina pectoris. The observations reported prove that this rule is *no longer tenable*. The electrocardiogram may be normal in both conditions, but it may also show marked alterations in patients with an ovarian insufficiency as well as those with a coronary disease.

Since it now has become possible to register objective findings in the group of patients, it is clear that the diagnosis "neurocirculatory asthenia" is inadequate. On the other hand, it was pointed out earlier that the diagnosis of some cardiac

disease frequently seemed justified in the past when the endocrine disturbance, just discussed, was actually present.

Formerly when a young woman complained of palpitation, of precordial pain, of tachycardia, and a systolic murmur was heard, if a rise of temperature was discovered, especially before the menses and the electrocardiogram showed some anomalies of the T-waves, an endocarditis accompanied by myocarditis was suspected. Not rarely these patients were kept in bed for months, the tonsils were removed and suspected teeth were extracted, sulfanilamide was given in doses which caused anemia and other signs of intoxication until late, often very late, the diagnosis was corrected.

Hypertension in a woman between the ages of fifty and sixty years with an altered electrocardiogram suggested coronary sclerosis, or *precordial pain* was deemed proof of the presence of angina pectoris. The diagnosis was understandable since these patients presented tachycardia of 100–120 and a rough systolic murmur over the aorta and apex is frequently heard. Since albuminuria and pitting edema of the ankles may appear in climacteric patients, treatment with digitalis is frequently initiated, the presence of cardiac decompensation being assumed. The fact that the *liver* of such a patient *is not enlarged* should convince the physician that a failure of the right heart does not exist. Mistakes, however, are common and easily understood.

Frequently *hyperthyroidism* is diagnosed. The sparkling eyes and the rapidity of movements, cardiac hyperexcitability, tachycardia, and increased basal metabolism suggest this diagnosis. Although the increase of basal metabolism is frequently due to the existing hypertension, other signs of hyperfunction of the thyroid are unmistakenly present. It is, however, usually forgotten that the hyperfunction of the thyroid is *the result* of the hypofunction of the ovaries, and consequently increased formation of thyrotropic hormone by the anterior hypophysis. Only a *symptomatic hyperthyroidism* is present, and treatment should be directed primarily against the *ovarian disturbance*.

In some patients with hypertension due to an ovarian insufficiency, damage of the heart muscle, combined with signs of hyperthyroidism and tachycardia, occasionally signs of acute

cardiac weakness, and even attacks of pulmonary edema, occur; they are especially common after a heavy meal with the ingestion of large quantities of fluid or after great physical exertion.

The injury of the heart muscle described also explains the sudden *decompensation* of female cardiac patients during the change of life. According to Kostkebitsch, it is the menopause which causes the decompensation in 25 per cent of women with organic heart lesions. Sudden cardiac failure in rheumatic heart lesions or in hypertensive patients during the critical age is common and now easily understood.

Treatment.—The administration of *estrogenic hormone* furnishes astonishing results; complete therapeutic success is regularly secured. The treatment of the disturbances described above has become one of the most satisfactory in therapeutics. As in all treatment with endocrine products, *individualization* of the dose is necessary. In the majority of cases *small* doses are sufficient.

Capsules or *rectal suppositories* of estrogenic hormone are usually prescribed; 2000–5000 units once a day are sufficient in most of the cases in spite of the fact that only a small fraction of the hormone administered in this way is utilized. Treatment should be continued for fifteen to twenty days. A definite improvement in the electrocardiogram occasionally is observed as early as the eighth day after treatment is begun.

Only in *very severe cases*, with marked hypertension, tachycardia and alterations of the electrocardiogram, must a series of six to ten injections, each containing 10,000–50,000 units, be given. Therapy should be continued until symptoms disappear and signs (electrocardiogram) are normal. In many cases the patient subsequently remains symptom-free without any further treatment over a long period. In other cases disturbances reappear sooner or later and it is necessary to supply maintenance doses for longer periods. This is accomplished by means of capsules.

Patients who *still menstruate* usually receive ten to fifteen capsules of 2000 units each, one daily beginning with the first day after the administration. In *younger patients*, the administration of the *gonadotropic hormone* of the anterior hypophysis often proves useful (Fig. 119).

CUMULATIVE INDEX